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CALCIUM AND PHOSPHORUS METABOLISM IN DISEASES OF THE THYREOPARATHYREOID APPARATUS.

PART I.

CALCIUM, PHOSPHORUS AND TOTAL METABOLISM IN HYPERTHYREOIDISM, AND THE PART PLAYED BY THE PARATHYREOID GLANDS.

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Historical.

THE first systematic studies on calcium and phosphorus metabolism in clinical hyperthyreoidism were carried out by Aub and his co-workers[6][8] at the Massachusetts General Hospital, Boston. From a survey of previous work on the subject, of which they give a summary,[8] they justly concluded that the evidence for anomalies in calcium and phosphorus metabolism was unsatisfactory and inconclusive. Aub and his co-workers carried out careful balance experiments with a low calcium, low phosphorus diet on several patients suffering from hyperthyreoidism, and were able to prove that there was a profound loss of calcium and phosphorus from the body. They compared the calcium and phosphorus metabolism in hyperthyreoidism and *osteitis fibrosa cystica generalisata*, showed that there were certain differences, and concluded that the negative calcium and phosphorus balance in hyperthyreoidism was most probably due to a specific effect on bone of the excess of circulating thyroxin, by means of which calcium was mobilized and excreted, predominantly in the fæces. Their conclusions, which have been widely accepted[5][39][66][63][44][121][80][67][122][123][98] and were still held by the Boston School as late as November, 1932,[124] are given *verbatim*:[8]

> Thyroid secretion has been shown to increase markedly calcium excretion. The cause of this is as yet undetermined. There are several possibilities:
>
> 1. A stimulating effect on the parathyroid glands directly or through their sympathetic innervation. The absence of any marked rise in the serum calcium is very much against this, although Hunter and Aub reported a case in which the administration of Collip's parathyroid

extract increased the calcium excretion without appreciably raising the serum calcium level. Work now in progress will probably determine this possible relationship.[1]

2. A method of neutralizing the acid products of an increased metabolism.

3. The remaining explanation, namely, a direct stimulating catabolic effect on the calcium deposits in the bones, seems the most likely one, and this would be in agreement with the general action of thyroid on other body tissues.

The loss of calcium found by the Boston School was out of all proportion to the elevation of the basal metabolism: in one case the excretion of calcium was 261% above the normal average, while the basal metabolism was 55% above normal; and other cases showed similar findings. The excretion of calcium, therefore, was not simply a manifestation of the increased metabolism. Further, they failed to find any increased calcium excretion in fever due to subacute bacterial endocarditis or lymphatic leuchæmia, but did find a greatly augmented loss in one case of myelogenous leuchæmia; in all these cases there was a definitely increased basal metabolism, and it was concluded that "an increased calcium excretion is not necessarily a function of an elevated metabolism."[(8)]

Both the Boston School and Donald Hunter in his review in *The Lancet*[(67)] and *The Quarterly Journal of Medicine*,[(66)] remark on the large losses of calcium in the fæces, which is in contrast to the findings in "hyperparathyreoidism", in which they state the increased calcium excretion is practically only in the urine.

Subsequent to their papers in 1929 the Boston School have further investigated the cause of the augmented calcium and phosphorus excretion, and have been able to exclude an acidosis as the cause,[(1)] and also the possibility of vitamin *D* lack.[(124)] As they practically excluded in their original paper the possibility of an associated hyperparathyreoidism, they are left with their third explanation, namely, "a direct stimulating catabolic effect on the calcium deposit in the bones"; or, as they say in a later paper,[(1)] "there may be a combination of several factors at work".

We were not satisfied that the Boston School and Hunter were justified in excluding the possibility of an associated hyperparathyreoidism, on the evidence they present. This evidence must be considered somewhat fully.

1. Firstly, they considered that the absence of an elevated serum calcium in hyperthyreoidism in contrast to the greatly elevated figure found in *osteitis fibrosa cystica generalisata* was evidence against an associated hyperparathyreoidism. Not every case of *osteitis fibrosa cystica generalisata* has shown high calcium figures; for example, a patient of Hunter[(69)] was examined four times and had serum calcium figures 12·1, 12·6, 11·2 and 13·6 respectively. Practically all the sixteen patients with adenomatous parathyreoidism described by Ballin and Morse[(10)] had serum calcium levels below 12 milligrammes *per centum*. In Lievre's[(81)] second case the serum calcium was 10·5 milligrammes *per centum*. In Compere's case[(37)] the serum calcium varied between 11·9 and 12·5 milligrammes *per centum*. In Wilder's case[(129)] the serum calcium varied between 11·2 and 11·4 milligrammes *per centum*. In Gold's case[(51)] the serum calcium was 13·1 milligrammes *per centum*. There is considerable variation in the normal values for calcium, according to the method and technique employed, and without the normal range for the laboratory being given, levels up to 12 milligrammes *per centum* cannot be accepted as pathological.

Calcium figures in hyperthyreoidism are not commonly given, but in the material of Aub and his co-workers, case Norman G.[(8)] had a serum calcium of 12 milligrammes *per centum* and case Emma F.[(1)] 11·8 milligrammes *per centum*. In a series of unselected hyperthyreoidic patients we found 11·5, 11·0, 11·1 and 11·4 milligrammes *per centum*. These figures are then comparable to those found in many cases of the "hyperparathyreoidism" of *osteitis fibrosa cystica generalisata*.

Injections of parathormone are stated to raise the level of the serum calcium; here again there are exceptions: in a case of Hunter and Aub[(65)] the serum calcium was not raised, and in a case of Albright, Bauer, Roper and Aub (Case III[(3)]) the calcium was never above 11 milligrammes per *centum* after the first few days of parathormone injections. Hunter's second patient with *osteitis fibrosa cystica generalisata*[(69)] after operation was given parathormone injections without the serum calcium being raised, and in one case of post-operative tetany at the Royal Prince Alfred Hospital, paroidin injections failed to cause any significant rise in serum calcium.

Experimentally profound changes in the skeleton and a negative calcium balance have been induced by parathormone injections without the serum calcium being elevated above normal limits; for example, Bodansky, Blair and Jaffe in guinea-pigs,[(22)] Jaffe and Bodansky in dogs,[(72)] Bodansky and Jaffe in dogs[(23)] and Morgan and Garrison in pups.[(87)]

True hyperplasia of the parathyreoid glands has been found in conditions such as rickets, osteomalacia and hunger osteopathies, as discussed by Dragstadt in his review,[(42)] by Schmorl,[(94)] by Barr and Bulger[(12)] and by Chick.[(34)] In these conditions a raised serum calcium is exceptional. It is generally low, so that hyperparathyreoidism *per se* need not necessarily cause a raised serum calcium. Grant and Gates[(52)] induced hyperplasia of the parathyreoid glands in rabbits by exposure to ultra-violet light, and say:

Emphasis should be placed on the fact that a parathyroid hypertrophy of 20% to 50% does not result in

[1] We have not been able to find any subsequent publication of such work, except that Donald Hunter[(67)] refers to unpublished data of Aub, Hunter, Hunter and Tibbetts, these data being of experiments on the administration of thyreoid extract to thyreoparathyrepidectomized cats and dogs which were unsuccessful, as the cats died in tetany and the dogs developed tetany within ten days.

a corresponding increase in the calcium content of the blood where the calcium concentration is already at or near the normal level.

It is evident that the absence of hypercalcæmia in hyperthyreoidism does not exclude the possibility of an associated hyperparathyreoidism.

As has been so frequently stressed, the level of serum calcium gives no information of the rate of flow. Provided mobilization and excretion or utilization proceed *pari passu*, there may be large shifts of a metabolite without any change in serum concentration.

2. Secondly, Aub and his co-workers consider, as is almost generally held, that there is a true hyperparathyreoidism in *osteitis fibrosa cystica generalisata*. So far practically every patient with *osteitis fibrosa cystica generalisata* who has been operated on[1] has had a tumour (so-called adenoma) of the parathyreoid gland.[69][70][29][10][90][83][4][110a][51][37][79][81][11] Hunter,[71] Lievre,[81] and Barr and Bulger[12] give summaries of published cases. Well authenticated cases in which at operation a tumour has not been found[63][85][28] (no operation or *post mortem* examination was performed, but no tumour was palpable in the neck) must not be necessarily excluded, because, as Walton[128] points out, the parathyreoid tumour may be in an unusual and inaccessible place.[2] The question of the nature of the tumour we do not feel competent to discuss. It has almost generally been described by the histologist making the report as having the "typical histology of a parathyreoid adenoma". Turnbull[71] will go no further than say that the tumours suggest a hyperplasia and excessive secretory activity rather than an autonomous neoplasm. If the extraordinary enlargement of the parathyreoid gland is not adenomatous, it is difficult to imagine that it is due to extrinsic stimulation, because it might be expected that the other parathyreoid glands would also enlarge. Whether the tissue is neoplastic or hyperplastic, the secretion produced by this tissue is able apparently to cause *osteitis fibrosa cystica generalisata*, an elevated serum calcium and a greatly augmented excretion of calcium, which is mostly in the urine. Whether the secretion of the parathyreoid tumour is the same as that of a normal parathyreoid gland or whether excess of the pure secretion of normal parathyreoid glands can cause *osteitis fibrosa cystica generalisata* awaits proof. It is well established that there are true adenomata of the thyreoid gland[43a][43a] and that the secretion therefrom can produce severe thyreotoxic symptoms without necessarily causing any elevation of the metabolism, and that the removal of these so-called toxic adenomata by simply "shelling" them out of their capsule will ameliorate the patient's condition. These "tumours" must produce a secretion which is not pure thyroxin, and it seems not unreasonable to suggest that the parathyreoid tumour produces a secretion which is not true parathyreoid secretion—we refrain from using the term "parathormone" because the secretion of the parathyreoid gland has not yet been isolated in crystalline form. In spite of the contention of Holt, La Mer and Chown,[64] that serum is supersaturated with $Ca_3(PO_4)_2$, made possible, as Greenwald and Gross think,[53] through the agency of the parathyreoid secretion, it has been abundantly shown[90][122][74] that even in the complete absence of parathyreoid secretion the serum calcium can be raised by vitamin *D* administration to extraordinary levels, for example, in the case of a dog reported by Jones, Rapaport and Hodes,[74] to as much as 47·27 milligrammes *per centum*; and in the same connexion Greenwald[55] illustrates the potent effect of sodium citrate in keeping calcium in solution; so that, as agencies other than true parathyreoid secretion can keep calcium in solution, it is not unreasonable to suppose that a pathological secretion of a parathyreoid tumour may be different from true parathyreoid secretion and yet have the power of keeping calcium in solution above that normally found in the serum.

As regards the production of *osteitis fibrosa cystica generalisata* being due to normal parathyreoid secretion circulating in excess, this has not yet been proved experimentally. Byrom[71] failed to produce anything more than *osteitis fibrosa* without cysts by injecting parathormone into rabbits, and though Bodansky and Jaffe,[23] and Bodansky, Blair and Jaffe[22] claim to have produced lesions of the nature of cysts in rabbits and dogs, Turnbull will not accept their findings without confirmation. It may be only a changed parathyreoid secretion that has the power to produce *osteitis fibrosa cystica generalisata*.

3. Thirdly, in regard to the distribution of calcium in fæces and urine in hyperthyreoidism and in *osteitis fibrosa cystica generalisata*, Aub and his co-workers,[6][58] Hunter[67] and Thomson and Collip[121] remark on the difference in distribution between the calcium in urine and in fæces in the two diseases. In *osteitis fibrosa cystica generalisata* the excretion of calcium is predominantly in the urine; in hyperthyreoidism, though the urinary calcium is increased, there is also a great increase in the calcium in the stool. However, the number of fully recorded balance experiments in *osteitis fibrosa cystica generalisata* is not large, but in these the urine has not always been the only or even the chief excretory channel; for example, in one of Hunter's cases[70] there was a definitely increased fæcal excretion, and in Lambie's case[79] the excretion was almost entirely in the fæces; but as this patient was on a solely milk diet it is highly probable that the calcium was not adequately absorbed.[46] In Wilder's case,[128] 59% of the calcium output was in the fæces.

The results of parathormone injection do not support the argument that an augmented fæcal excretion of calcium in hyperthyreoidism is evidence

[1] The references quoted are incomplete, but the cases number about thirty in all.

[2] Bauer[13a] reports that the patient originally reported by Du Bois and subsequently by the Boston workers was operated on seven times before a parathyreoid tumour which was substernal could be found.

against an associated hyperparathyreoidism. In one publication from the Boston School[3] the results of parathormone injections in a series of six cases are described. Unfortunately protocols are not given, but by calculation from their diagrams four cases, Cases II, III, IV and V, show a very marked fæcal excretion of calcium in addition to an increased urinary excretion, while parathormone injections formed the sole means of treatment. In Case II the fæcal calcium rose from approximately 0·09 to 0·63 gramme per day (patient a male, aged fourteen, with symptoms of otosclerosis). In Case III, from approximately 0·08 to 0·92 gramme per day (coloured boy, aged fourteen, suffering from an ossifying hæmatoma of right thigh), and in this last-mentioned case, except for the first few days, the continued injection of parathormone failed to raise the serum calcium above 10·5 milligrammes *per centum*, though the loss of calcium through the urine and stool continued.

Experimentally it has also been found that parathormone causes an increased excretion of calcium in the fæces in cats and dogs, Stewart and Percival;[113] in dogs, Greenwald and Gross;[54][56] and in rats, Pugsley.[91] Apparently, once mobilized, calcium is excreted in both urine and stool; which of the two is to be the main path of excretion depends on factors other than those primarily responsible for its mobilization. It is quite conceivable that the increase of fæcal excretion in hyperthyreoidism may be partly due to changes of vascularity or motility or excretory activity of the alimentary tract, or physico-chemical changes in the body fluids[99] induced by the raised metabolism.

4. Fourthly, from their results of thyroxin injections Aub and his co-workers deduce further evidence for a specific effect of thyroxin on mobilizing calcium. They found[8] that injections of thyroxin in myxœdema and in normal people increase calcium excretion. In their myxœdematous patients the increase in calcium excretion was not of great magnitude, and was almost entirely in the urine in each of the six patients experimented upon; their results on two normal patients were similar, so that these cases can hardly be used in evidence that thyroxin has a specific effect in mobilizing calcium from the bones and augmenting fæcal excretion. Boothby[40] gave thyroxin to a normal person on a protein-free diet, and raised the metabolism 20% without effecting any change in calcium excretion.

Aub and his co-workers[7] also tried the effect of thyroxin in one patient suffering from post-operative hypoparathyreoidism and one patient suffering from idiopathic tetany. From their results they concluded "that thyroxin results in a marked elevation of the blood calcium, but that the elevation of the blood calcium does not lead to increased calcinuria until the blood calcium has risen beyond the threshold level". A threshold for calcium excretion in the urine may or may not exist, but no one has postulated a fæcal threshold for calcium, and as the thyreoid hormone is supposed by the Boston School to favour excretion through the bowel of the calcium it has mobilized from the bones, their results in these two cases are really against their hypothesis, as thyroxin in these cases caused only an augmented urinary excretion. In Case I parathormone was given along with the thyroxin, so that conclusions as to the effect of thyroxin alone are not permissible. In Case II thyroxin caused an elevation of the serum calcium from 4·5 to 6·4 milligrammes *per centum*, but this may easily be explained as being secondary to a stimulation of the parathyreoid glands by thyroxin.

On the whole, therefore, though their experimental work is suggestive, it is by no means conclusive, and throughout there is the strong possibility that an associated hyperplasia of the parathyreoid glands is actually the cause of the anomalies in calcium and phosphorus metabolism. We shall offer experimental evidence in favour of an associated hyperparathyreoidism: firstly, from the changes in calcium and phosphorus excretion following the application of therapeutic X rays to the neck in hyperthyreoidism (five cases); secondly, from the nature of calcium and phosphorus metabolism in hypoparathyreoidism associated with hyperthyreoidism[1] (two cases); thirdly, from the general independence of calcium and phosphorus metabolism and the total metabolism in hyperthyreoidism.

Ward and Laboratory Methods.

The Board of Directors of the Royal Prince Alfred Hospital kindly placed at our disposal a small private ward, with a special dietary kitchen, in which we were able to study two patients at a time. We had the services of a full-time sister and a full-time nurse. Without facilities at least as good it would be impossible to carry out such an investigation. We modelled our plans somewhat after those of the Massachusetts School.[16]

Periods on the whole were of four days, but at times three-day and five-day periods were used. Each period began in the morning before breakfast, and the fæces were marked off by a carmine lake capsule. The regularity with which the indicator appeared in several patients within twelve hours of being taken, seems to call for some modification of our ideas of the rate at which ingested material may pass along the gut. Great care was taken to separate the red portion from the uncoloured portion in those stools which were composed of fæces partly of the previous and partly of the subsequent period.

In contrast to the diet used by Aub, the diet was such that constipation was present only in the two control patients, both of whom had always required aperients. In one of the controls the bowels moved almost regularly during the whole month she was an experimental subject, while previously she had been a martyr to constipation. When aperients

[1] Ask-Upmark[69] has recently reviewed the literature on the occurrence of hypoparathyreoidism associated with hyperthyreoidism.

were required, uncoated "Alophen" pills were used. Enemata were never employed. Gross error results when they are used to obtain a stool if the carmine does not appear within twenty-four hours, as was the practice of the Massachusetts workers. When so used, an enema in their three-day period could cause errors of +30% or –30%. We found that the carmine coloured stool was almost invariably loose.

As mistakes are liable to occur at odd times, such as at night or when a nurse is being changed or relieved, certain precautions were taken to insure the saving of all urine and to avoid loss of or mistakes in fæcal specimens. As regards urine, we had alongside each bed a box containing a Winchester, on which was written the patient's name, and a funnel above the box leading into the Winchester. All urine voided was then poured directly into the bottle under the supervision of the patient, whose cooperation was very valuable and very much appreciated. The stool was passed onto special paper, on which the patient previously wrote her name, the date and the time.

Urine.—Early in the research each twenty-four hour specimen of urine was preserved over powdered thymol; this was not very efficient in stopping bacterial growth at room temperature, but was better at lower temperatures. Later formalin was used and found much more satisfactory. At the completion of the twenty-four hour sample—9 a.m. to 9 a.m.—the volume was ascertained and one-tenth was taken and kept. The tenth-samples of the period were thoroughly mixed together and kept in an ice-chest awaiting analysis.

Fæces.—While we waited for the completion of a period the fæces were kept in an incubator at room temperature. The total stools for the period were carefully transferred to glass trays and dried in an electric oven, which cut out automatically at 140° C. It usually took twelve hours to dry the fæces sufficiently. The oven must be in an efficient fume cupboard. As far as we could ascertain by control experiments, there is no appreciable loss of nitrogen on heating organic material to 140° C. When thoroughly dried, the stools for the period were ground in a grinding mill, thoroughly mixed and weighed, and some 30 grammes were taken for sampling. These 30 grammes were ground in a mortar and made to pass through a 40-mesh sieve. Portions of this were then taken for analysis, as described under chemical methods.

Diet.

In metabolism experiments the choice of diet is always of great importance, but especially so in hyperthyreoidism. The principles of the experimental diet must be considered in detail, and we wish to stress what has been remarked upon by various experimental workers[15][115][82][45][101] concerning caloric and nitrogen requirements, acid-base balance, salt content, attractiveness, *et cetera*. The diet employed by Aub and his co-workers is open to criticism on several grounds. Each patient had to limit his diet to about twelve articles, which were given day in and day out during the experimental period; such a diet from its monotony must have a considerable psychic effect on hyperthyreoidic patients. The patients of Aub and his co-workers were allowed to eat as much as they wished, but a loss of weight and negative nitrogen balance of significant magnitude were the rule. The calcium loss in their hyperthyreoidic subjects was compared to that in normal subjects who were themselves in negative calcium balance. The diet of the hyperthyreoidic patients contained the same small amount of calcium (0·1 gramme per day) as that of the normal controls, but on account of the larger caloric requirements the ratio of calcium to phosphorus, nitrogen and total calories was very much smaller. This difference in the relationship of calcium to the other constituents of the diet is of importance, and would tend to encourage a negative calcium balance and influence the excretory path of calcium and phosphorus. Givens[49] from experiments on dogs concluded that diets poor in calcium are not conducive to positive calcium balance experiments even when an abundance of nitrogenous food is available. Shohl and Bennett[107] and Shelling[97] stress the point that the ratio of calcium and phosphorus in the diet of experimental animals influences the path of excretion of these elements.

We decided that the diet should be as normal and as attractive as possible, and that it should contain an optimum caloric-nitrogen-calcium-phosphorus ratio, which would remain constant with changes in the caloric value of the diet; in other words, a diet of 2,000 calories would have half the nitrogen, calcium and phosphorus of a 4,000-calorie diet. All patients had the same components in the diet. We aimed to keep our patients in slightly positive nitrogen balance and gaining weight slowly; to the adolescent patient, Marjorie R., we gave a diet large enough to enable her to make a more rapid gain in weight.

The experimental diet as far as possible should be a neutral diet. Our diet when balanced according to Sherman's figures[100] for fixed acid and base, was practically neutral. (See Table XII.) The ash was always slightly alkaline. The effect of an acid diet in causing an increased calcium excretion has been frequently stressed.[15][9][50][24][115] The effects of an alkaline diet are less obvious,[14][110] but there seems little justification for adding alkali to an experimental diet till the urine becomes alkaline, as Hunter[68][70] has recently done; normally in health the twenty-four hour urine is at least somewhat acid, and adding alkali to the diet till the urine is alkaline must influence the excretion of alkali through the large intestine. Bogert and Kirkpatrick[24] found that a base-forming diet increased the calcium output in the fæces. The fæcal ash from all our subjects, normal or otherwise, was always somewhat alkaline.

In Table XIII is given a list of the foods employed, and their relative amounts. By varying the methods of cooking, considerable variety of

TABLE XII.

Showing Acid-Base Balance of Diet.

Figures calculated from Sherman and Getler.[100]

	Grammes in Diet.	Excess acid or base in terms of normal solution. Per 100 grammes.		Excess acid or base in terms of normal solution. Per quantity in diet.	
		Acid.	Base.	Acid.	Base.
Sugar ..	120				
Butter ..	120	0·50[a]		0·60	
Bread ..	240	6·54[b]		15·70	
Oatmeal ..	24	12·93		3·10	
Milk ..	150		2·37		3·56
Pineapple ..	150		6·93[a]		10·39
Tomato ..	60		5·34[a]		3·20
Orange juice	90		5·61		5·05
Banana ..	75		5·56[c]		4·17
Lettuce ..	60		7·37		4·42
Beef ..	150	12·0		18·0 } Av.	
Fowl ..	150	17·0		25·5 } 21·5	
Fish ..	150	13·9[c]		20·85 }	
Apple ..	100		3·76		3·76
Cabbage ..	45		5·70		2·57 } Av.
Spinach ..	45		23·0		10·35 } 6·46
Potato ..	150		6·8[c]		10·20
Beans ..	60		5·6[a]		3·36
Jam ..	35				
Egg ..	120	11·1		13·32	
Total ..				55·2	54·57

[a] Calculated as flour.
[b] Average of three sets of calculations.
[c] Average of two types of fish.
[d] Calculated from ash constituents: Sherman, "Chemistry of Food and Nutrition", 1928.

dishes was obtained. We took as a basis a diet of 2,500 calories which was to contain 0·5 gramme calcium, 0·8 gramme phosphorus, and 60 grammes protein.

Calcium Requirements.—Sherman states[101][103] that 0·45 gramme calcium daily should be considered the minimal requirement for a man of 70 kilograms. Taking a man aged 30 and 165 centimetres in height, and using Dryer or Harris and Benedict's prediction tables[43] the basal requirements of such a man would be approximately 1,650 calories for twenty-four hours, and the maintenance requirements (basal × $^3/_2$) approximately 2,500 calories, so that minimal calcium requirement for 2,500 calories is 0·45 gramme.

As regards availability of calcium in different foods, it is now generally agreed[101][115] that all food calcium is converted into calcium chloride in the alimentary tract, and absorbed as such, so that the source of calcium is of no consequence.

Phosphorus Requirements.—For phosphorus we were also guided by Sherman's work,[102] but, as he points out, we have no proof as to whether the different compounds of phosphorus are equally valuable to the organism. From an analysis of all available data he gives 0·88 gramme phosphorus

TABLE XIII.

Diet for 3,500 Calories—Calculated values for various constituents.

	Actual Weight in Diet Grammes.	Estimated Carbohydrate.		Estimated Protein.		Estimated Fat.		Calories.		Calcium.		Phosphorus.	
		Percentage.	Amount in Diet.	Percentage.	Amount in Diet.	Percentage.	Amount in Diet.	Per Pound.	In Diet.	In 100 Grammes.	In Diet.	In 100 Grammes.	In Diet.
Sugar	120	100·0[a]	120·0	—	—	—	—	1860·0[a]	492·0	0·000[a]	—	0·000[a]	—
Bread	220	53·1[a]	117·0	9·2[a]	20·2	1·30[a]	2·9	1215·0[a]	589·0	0·027[e]	0·059	0·093[e]	0·205
Oatmeal	24	67·5[a]	16·2	16·1[a]	3·9	7·20[a]	1·7	1860·0[a]	98·4	0·069[e]	0·017	0·392[e]	0·094
Butter	145	—	—	1·0[a]	1·45	85·0[a]	123·0	3605·0[a]	1152·0	0·013[e]	0·188	0·014[e]	0·020
Apple	150	4·7[b]	7·05	0·4[a]	0·6	0·5[a]	0·75	116·0[g]	38·4	0·007[e]	0·011	0·012[e]	0·018
Pineapple ..	150	9·9[b]	14·9	0·4[a]	0·6	0·3[a]	0·45	204·0[g]	67·4	0·018[e]	0·027	0·028[e]	0·042
Milk	280	5·0[a]	14·0	3·3[a]	9·2	4·0[a]	11·2	325·0[a]	200·7	0·120[a]	0·34	0·093[e]	0·26
Egg	80	—	—	13·4[a]	10·7	10·5[a]	8·4	720·0[a]	127·0	0·067[e]	0·054	0·180[e]	0·144
Tomato (canned)	90	2·4[b]	2·16	1·2[a]	1·08	0·2[a]	0·18	75·0[g]	14·9	0·011[e]	0·010	0·026[e]	0·023
Beans (string) ..	80	1·3[b]	1·04	0·8[a]	0·64	1·1[a]	0·88	95·0[g]	16·7	0·046[e]	0·037	0·052[e]	0·042
or Cabbage ..	70	1·2[b]	0·84	1·6[a]	1·12	0·3[a]	0·21	65·0[g]	10·0	0·045[e,f]	0·032	0·029[e]	0·02
or Meat { Beef ..	150	—	—	20·9[a]	31·4	13·7[a]	20·6	965·0	320·0	0·012[f]	0·018	0·216[f]	0·324
or Meat { Fowl ..	150	—	—	19·3[a]	28·9	16·3[a]	24·5	1045·0	346·0	0·012[i]	0·018	0·216[i]	0·324
or Meat { Fish ..	150	—	—	18·0[a]	27·0	11·0[a]	16·5	799·2	264·2	0·022[i]	0·033	0·230[i]	0·345
Banana	75	18·7[b]	14·0	1·3[a]	0·98	0·6[a]	0·45	397·3[g]	65·7	0·009[e]	0·007	0·031[e]	0·023
Potato	170	19·2[b]	32·6	2·2[a]	4·25	0·1[a]	0·17	440·0[g]	165·0	0·014[e]	0·024	0·058[e]	0·10
Lettuce	60	0·7[b]	0·42	1·2[a]	0·72	0·3[a]	0·18	48·2[g]	6·4	0·043[e]	0·026	0·042[e]	0·025
Orange juice ..	90	6·1[b]	5·5	0·8[a]	0·72	0·2[a]	0·18	136·8[g]	27·1	0·029[e]	0·026	0·016[e]	0·014
Jam	35	84·5	29·6	0·6[a]	0·21	0·1[a]	0·04	1585·0	122·5	0·006[h]	0·002	0·006[h]	0·002
Water										0·00018[j]		0·000[j]	
Salt	5									0·058[k]	0·003	0·000[k]	
Calculated Total					87·77				3513·0		0·712		1·122
Estimated Total					76·7[x]						0·691[y]		1·176[y]

[a] "The Composition of American Food Material": Atwater and Bryant, Bulletin No. 28, 1906.
[b] "Available Carbohydrates of Foods": McCance and Lawrence, Medical Research Council, Special Report Series, No. 135, 1929.
When there is a significant difference between the carbohydrate values as given by Atwater and McCance, the value of the latter investigator is used for the carbohydrate, and the total caloric value per pound as given by Atwater is adjusted, using a fuel value of 4·1 calories per gramme for carbohydrate and protein and 9·3 calories per gramme for fat. Foods so calculated are denoted by the letter "*g*".
[c] "Chemistry of Food and Nutrition": Sherman, Third Edition, 1928, Appendix B.
[d] Analyses of the sugar used showed no appreciable calcium or phosphorus.
[e] Analyses of samples of butter, as described in text, gave the following successive values: 10·2, 12·4, 11·0, 12·0, 18·0, 14·0, 13·7, 9·8, 8·1, 11·6 milligrammes calcium per 100 grammes, and 14·0, 15·0, 13·0, 17·0, 14·0, 14·0, 14·0, 12·6, 10·7, 14·1 milligrammes phosphorus per 100 grammes.
[f] For a discussion on the variations in calcium content in cabbage, see Cowell (38).
[g] See above, under *b*.
[h] Analysis of a mixture of 50 grammes each of the three different jams used.
[i] Estimated on 20% protein, see "Chemistry of Food and Nutrition", Sherman.
[j] Analysis of three litres of Sydney tap water.
[k] Analysis of sample from salt used.
[l] Calculated as rump steak.
[x] Average of estimations on twelve four-day periods.
[y] Average of all estimations.

a day for a person of 70 kilograms, that is, for a 2,500 calorie diet. Our calculated figures are somewhat lower, but figures from actual analysis were satisfactorily close.

Nitrogen Requirements.—The problem of nitrogen requirements in hyperthyreoidism is a vexed one, but need not be discussed here. After consulting Lusk,[82] Sherman,[101][103] Greenwald[45] on nitrogen requirements in health, and Boothby's work on the subject of "The Total and Nitrogenous Metabolism in Exophthalmic Goitre"[27] we decided to work on a basis of 60 grammes of protein for a 2,500 calorie diet. Boothby gave varying amounts of protein to the same and different patients; the average was 66·6 grammes of protein for a 2,500 calorie diet, but most of his patients were in greater positive nitrogen balance than we aimed at producing.

Vitamins.—We wished to insure an adequacy of each vitamin without an excess of vitamin *D*. The distribution of vitamins according to the Medical Research Council's most recent list[126] was found to be satisfactory.

Method of Calculating Requirements for the Individual Patient.—On admission to the metabolic ward the caloric requirement was calculated as $^3/_2 \times$ basal, and the first few days were used to adjust this diet to the patient's appetite; the experiment was not begun until the diet was so adjusted. Generally very little adjustment was required. In some of the patients the diet was readjusted according to the rise and fall in the basal metabolic rate or the effect of treatment on the appetite; vitamin *D* increased the appetite in the two subjects to whom it was given. Changes in the diet were generally made at the beginning of a period. On the whole we had very little trouble in getting the subjects to eat all the food; one patient (Darcia T.) vomited on two occasions. If the patient was tending to lose weight, the diet was increased without her knowledge—a plan which we found more effective than inquiring too closely into the appetite and whether she could "eat a little more". Changes in the diet were made in every article in the diet proportionately, but as every article had to be weighed, this did not mean more than changing the weight.

Method of Preparing Food for Consumption.—We prepared lists of the weights of each article in a given caloric diet, and each article was weighed before cooking to an accuracy of 1%. It was then as far as possible cooked and served in the same vessel. Vegetables were cooked by steaming, and the resulting fluid was made into gravy.

Method of Preparing Food for Analysis.—We decided at the outset to estimate the nitrogen, calcium and phosphorus in the diet of each period. We continued to analyse for calcium and phosphorus, but at the end of several months, as the nitrogen in the food was not varying more than $\pm$ 5%, we took an average figure for nitrogen.

As regards calcium and phosphorus, most investigators use Sherman's figures. These are quite accurate as average figures, but the calcium and phosphorus content of any foodstuff may vary greatly; for example, Cowell[38] showed that in the case of cabbages there was a range from 1,058 milligrammes per 100 grammes for the outermost leaf to 32 milligrammes per 100 grammes for the heart leaf in the same cabbage; the calcium content of leaves used for human consumption ranged from 71 milligrammes to 26 milligrammes per 100 grammes. Bogert and Kirkpatrick[24] found that in certain diets the true calcium content (found by analysis) was as much as 30% higher than the calculated figure. Bauer and Aub[16] give a list of the calcium content of various substances as found by themselves, by Sherman and by Keith. To take two common articles used in large amounts in their diets:

Calcium per 100 grammes of foodstuff.

	Bauer and Aub	Sherman	Keith
Bread	0·041	0·027	0·040
Bacon (boiled)	0·030	0·007	0·006

Bassett, Elden and McCann[13] found that the calcium as estimated was 15·5% below Sherman's figures.

Again, a metropolis such as Sydney obtains its food supplies from localities having great variation in season, temperature, rainfall and soil. Such factors must influence the salt content of vegetables, fruit, milk, butter, *et cetera*. On a low calcium diet variations, as Aub and his co-workers point out, are not of great moment, but in the diet employed by us the possibility of large errors was too real to allow the use of average figures.

The following foods were obtained in bulk and analysed once for each large quantity:

Butter was analysed in thirty pound lots, 100 grammes from each lot were filtered by hot filtration through an ash-free paper. The paper and contents were ashed, dissolved in 10% hydrochloric acid, made up to a volume of 20 cubic centimetres, and analysed for calcium and phosphorus. The values obtained are given in an appendix.

Sugar was analysed once by ashing, and found to be calcium-free and phosphorus-free.

Jam of the same date of manufacture was obtained in bulk; 150 grammes were dried and ashed. The ash was dissolved in 10% hydrochloric acid, made up to volume and analysed, and was found to contain 0·006 gramme calcium per 100 grammes and 0·006 gramme phosphorus per 100 grammes.

The ordinary tap water was used. It is a very soft water. Three litres were evaporated to small bulk, and organic matter was destroyed by acid hydrolysis. Analysis gave calcium 0·0018 gramme per litre and no phosphorus.

The remaining articles were analysed by taking samples each day and analysing every period. For convenience in weighing, one-tenth of the amount present in a 3,500-calorie diet was weighed to an accuracy of 0·1 gramme *per centum*, and all the ingredients were mixed on a plate-glass slide of suitable size (the bread acting as an adequate sponge for the fluids) and heated in an ordinary

gas oven at a temperature below 140° C. till dry. The mass was carefully scraped off with a knife, then ground finely in a mill, thoroughly mixed and weighed. Thirty grammes by weight were taken and ground in a mortar and made to pass through a forty-mesh sieve. By various checkings we have satisfied ourselves that the variations in calcium and phosphorus content found by analysis are real, and not due to errors in sampling or analysis.

Milk was always thoroughly mixed before the sample was taken for analysis. The yolks and whites of the eggs for the day's use were always thoroughly beaten together and then samples were taken for analysis. In sampling fruit and vegetables care was always exercised to obtain representative samples. Water was given as water or as tea. We allowed 1·2 litres per 3,000 calories, and found that in general it satisfied the patient's requirements. (For methods of analysis see appendix.)

Experimental Data.

Normal Controls.

Two subjects were studied as normal controls. Both were in calcium, phosphorus and nitrogen equilibrium on the diet calculated from their actual basal metabolism. The results obtained were comparable to those of Sherman,[105][106] Rose,[93] Bogert and McKittrick,[25] and Bogert and Kirkpatrick[24] on similar diets.

Gwen P., aged twenty-five, a female, single, was a nurse who volunteered for the experiment. The estimated caloric requirement (basal × 3/2) = 1,900 *per diem*. The caloric intake was 2,100 for first period; 1,870 for remaining periods. Fluid intake was 800 cubic centimetres daily. (For experimental details see Table I and Graph I.)

The average calcium intake was 0·398 gramme *per diem*, the average output was 0·346 gramme *per diem*.

The average phosphorus intake was 0·626 gramme *per diem*, the average output was 0·658 gramme *per diem*.

The average nitrogen intake was 6·60 grammes *per diem*, the average output was 6·01 grammes *per diem*.

She was in positive calcium balance for six out of seven periods.

She was in positive phosphorus balance for two out of seven periods—a range of −0·12 gramme to +0·07 gramme *per diem*.

She was in positive nitrogen balance for five out of seven periods.

Joan H., aged twenty-one, female, single, was a patient convalescent after an operation for double inguinal hernia. The experimental period began nine days after operation. The estimated caloric requirement (basal × 3/2) = 2,000 *per diem*. The caloric intake was 2,330 *per diem;* the fluid intake 900 cubic centimetres daily. (For experimental details see Table II and Graph II.)

The average calcium intake was 0·44 gramme *per diem*, the average output 0·517 gramme *per diem*.

The average phosphorus intake was 0·78 gramme *per diem*, the average output 0·691 gramme *per diem*.

The average nitrogen intake was 8·07 gramme *per diem*, the average output 6·70 grammes *per diem*.

She was in positive calcium balance for none out of four periods, a range of −0·01 gramme to −0·08 gramme *per diem*.

She was in positive phosphorus balance for three out of four periods.

She was in positive nitrogen balance for four out of four periods.

TABLE I.

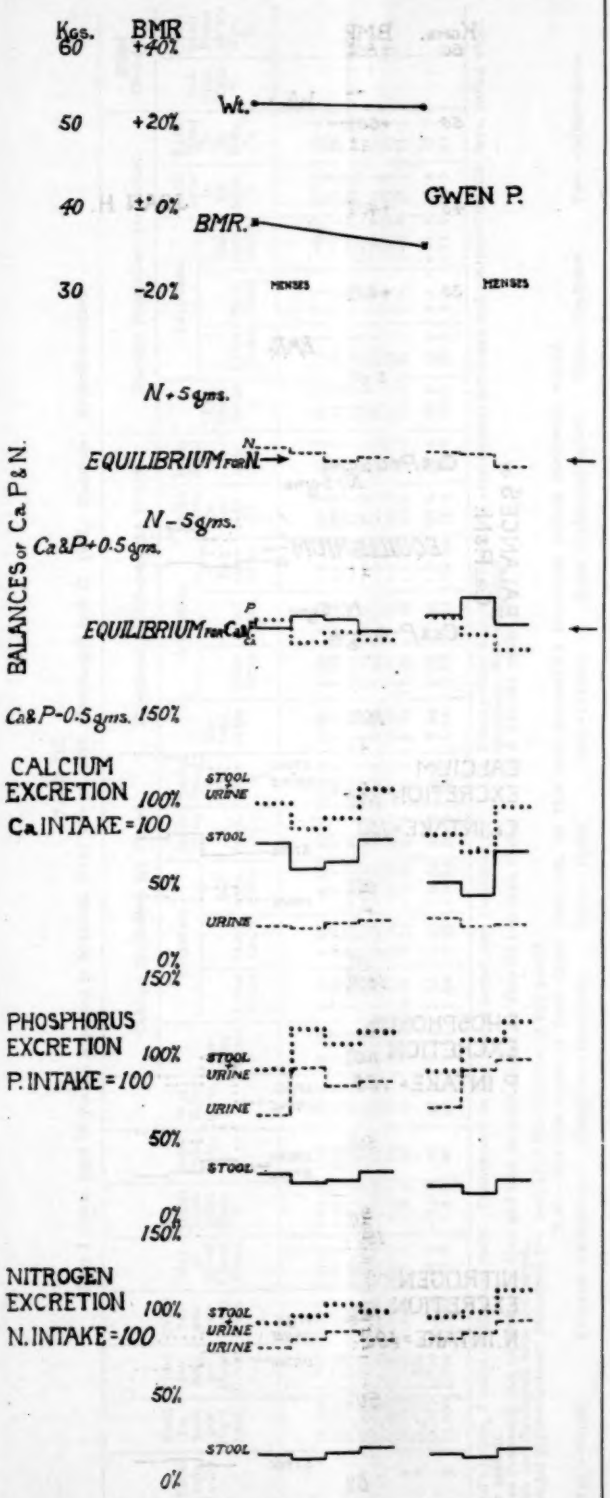
Gwen P., female, single, aged 25 years. Admitted to Metabolic Ward October 4, 1932. Discharged November 10, 1932. Diagnosis: Normal Control.

Period Number.	Footnote Index.	Food Intake per Per'd. Cals.	Fluid Volume per Diem. C.cm.	Urine Volume per Per'd. C.cm.	Stool Wgt. per Per'd. Grms.	Basal Metabolic Rate. %	Basal Pulse Rate.	Wgt. Kilogrms.	Calcium Metabolism per Period.					Phosphorus Metabolism per Period.					Nitrogen Metabolism per Period.					Blood Chemistry.	
									Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Excretion. Balance. Grms.	Ratio Urine to Intake. %	Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Excretion. Balance. Grms.	Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Excretion. Balance. Grms.	Ratio Urine to Intake. %	Ratio Stool to Intake. %	Calcium. Mgm. %	Inorganic Phosphorus. Mgm. %
0	1	4,200	800	3,720	65·3			52·3	1·56	0·39	1·14	+0·08	25·0	73·1	1·69	0·77	+0·25	62·4	28·4	29·5	22·7	4·2	+2·6	77·0	14·2		
1	2	8,400	800	2,840	52·8				1·53	0·37	0·88	+0·28	24·7	57·5	2·33	0·57	+0·34	90·1	24·5	29·5	21·6	3·3	+1·3	82·5	12·6		
2	2	7,470	800	5,705	59·5				1·72	0·46	1·07	+0·19	26·7	62·2	2·46	0·61	−0·13	86·5	24·8	29·2	22·7	3·6	−0·03	86·6	14·5		
3	2	7,470	800	2,900	70·0				1·58	0·44	1·19	−0·05	27·8	75·3	2·45	0·73	−0·30	82·5	29·8	29·2	21·1	4·7	+0·04	80·5	17·9		
4	3	7,470	800	3,640	52·5	−4·3	72		1·49	0·42	0·74	+0·33	28·2	49·7	2·49	0·54	+0·39	66·7	21·7	26·2	21·4	3·4	+1·4	81·7	13·0	10·4	4·39
5	4	7,470	800	3,080	46·7	−10·0	72	51·6	1·72	0·41	0·73	+0·68	23·8	42·4	2·51	2·24	+0·17	89·2	17·5	26·2	22·2	2·9	+1·1	84·7	11·1		
6	5	7,470	800	3,440	67·5				1·55	0·40	1·06	+0·09	25·8	68·4	2·59	2·44	−0·46	94·2	29·2	29·2	24·3	4·3	−2·4	92·8	16·4		

1 On experimental diet for two days—specimens not saved.
2 Menses began on third day and continued for six days.
3 Four days' spell—not on strict experimental diet.
4 On experimental diet again.
5 Nervous and upset, and nausea. Final examination for Australasian Trained Nurses' Association imminent.

N.B.—Periods were of four days' duration, in this and succeeding protocols, unless otherwise stated.

Wgt. = Weight. Kilogrms. = Kilograms. Phosph'us = Phosphorus. Per'd. = Period. Cals. = Calories. C.cm. = Cubic centimetres. Grms. = Grammes. Mgm. = Milligrammes.



GRAPH I.

Gwen P., female, single, aged twenty-five. Diagnosis: normal control.

Hyperthyreoidic Patients.

Patients Treated with Iodine.—Two patients were treated solely with iodine during the experimental study.

CASE I.—Albert I. was a male aged thirty-eight. (For history see case report.) The estimated caloric requirement (basal × 3/2) = 3,480 *per diem*. The actual caloric intake was 4,080 *per diem*. The fluid intake was 1,800 cubic centimetres *per diem*.

This subject of all our patients showed the greatest discrepancy between the calculated requirement and that which satisfied the appetite. (For experimental details see Table III and Graph III.)

Fore-period.[1]—Three four-day periods, rest in bed, no medication.

Iodine Therapy.—Four four-day periods; Lugol's iodine, three cubic centimetres, was given daily. The patient then had a subtotal thyreoidectomy. This was followed by two further experimental four-day periods, beginning twenty-three days later.

Metabolism During Fore-period.—Basal metabolism was constant in the vicinity of +35%. The weight was constant at 50·5 kilograms. The nitrogen balance was very slightly negative, average −0·87 gramme daily. The phosphorus balance was definitely negative, average −0·28 gramme *per diem;* range −0·27 to −0·34 gramme *per diem*. The calcium balance was definitely negative, average −0·348 gramme *per diem;* range −0·268 to −0·395 gramme *per diem*.

Metabolism During Iodine Therapy.—The basal metabolism after a lag of four days fell rapidly, to reach a minimum of +6% on the seventh day, and then remained constant till operation on the seventeenth day. Weight increased progressively and followed the nitrogen retention fairly closely. He gained three kilograms in fourteen days.

Nitrogen balance became positive during the first four days. Nitrogen retention then proceeded at a progressive rate, though the diet and basal metabolic rate remained constant.

Phosphorus balance, from being definitely negative, showed an immediate improvement, and during the first period the negative balance was only 0·07 gramme *per diem;* the balance then became positive during the second period, and phosphorus retention progressed during the third and fourth periods. Changes in phosphorus followed the nitrogen balance and preceded changes in the basal metabolic rate and calcium metabolism.

[1] Fore-period is used to denote that stage of the experiment which preceded any medication. The patients were in bed and were having the experimental diet. Three, four or five-day period is used to denote the number of days over which the food, urine and stool were respectively added together for analysis.

Explanatory Notes for Graphs I to XI.

B.M.R. = basal metabolic rate, which is graphed on the actual day the estimation was carried out. This detail is not given in the protocol.

Wt. = weight in kilograms and was always taken fasting and in the same garment.

Balance of Ca, P, and N = the difference in grammes *per diem* between the intake and excretion, ascertained by dividing the difference in grammes per period by the number of days in the period. When the intake is greater than the excretion, the balance is positive and appears above the line representing equilibrium. When the excretion is greater than the intake, the balance is negative and appears below this line. If the balance of N tends to run into that of Ca and P it is graphed with a separate equilibrium line.

Scale for Ca and P: one gramme = two inches on the original graph.

Scale for N: ten grammes = one and a half inches on the original graph.

One day = one-tenth of an inch on the original graph.

Menses: The letters are spaced to cover the actual number of days menstruation lasted.

Excretion of Ca, P, and N: The amounts of Ca or P or N excreted in the urine, stool and the total excretion (urine + stool) are graphed as a percentage of the intake so that the intake is always 100. The intake varied slightly from period to period, and by graphing as a percentage the graph is smoothed out and can be read with greater facility.

Scale for excretion of Ca, P, and N: 0% to 100% = two inches on original graph.

TABLE II.

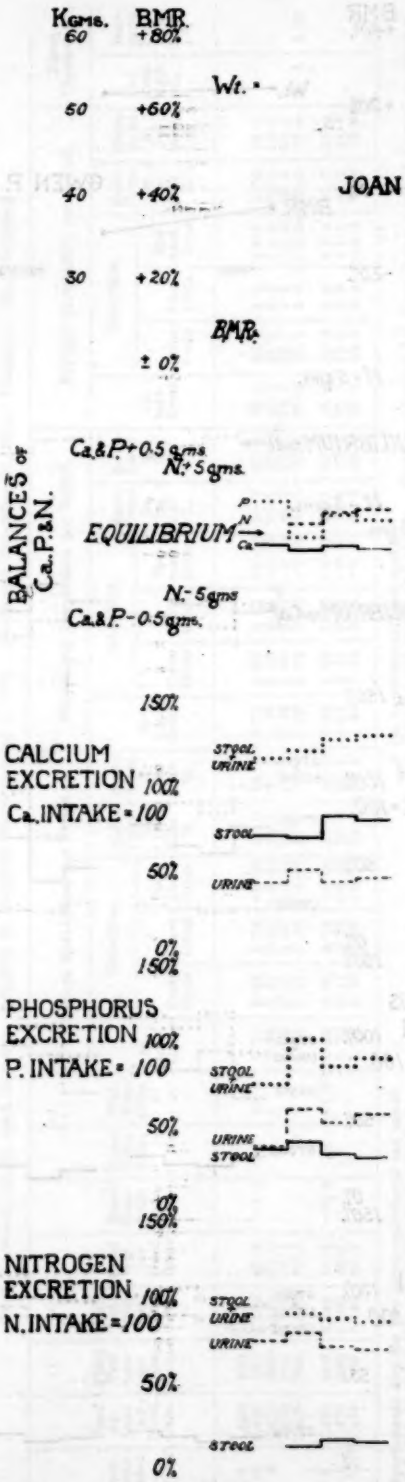
Joan H., female, single, aged 21 years. Admitted to Metabolic Ward June 22, 1932. Discharged July 11, 1932. Diagnosis: Normal Control.

Period Number.	Food Intake per Per'd. Cals.	Fluid Intake per Diem. C.cm.	Urine Volume per Per'd. C.cm.	Wgt. of Dried Feces. Grms.	Basal Metabolic Rate. %	Basal Pulse Rate.	Wgt. Kilogrms.	Calcium Metabolism per Period.					Phosphorus Metabolism per Period.					Nitrogen Metabolism per Period.					Blood Chemistry.	
								Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Balance. Grms.	Ratio Urine to Intake. %	Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Balance. Grms.	Ratio Urine to Intake. %	Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Balance. Grms.	Ratio Urine to Intake. %	Ratio Stool to Intake. %	Calcium. Mgm. %	Inorganic Phosphorus. Mgm. %
1	4,660	900	2,555	59·0	+7·0		53·0	1·72	0·77	1·20	−0·25	44·8	3·20	1·22	1·21	+0·77	38·1	31·0	23·4	4·02	+2·8	74·0	18·1		
1	9,320	900	2,480	65·5				1·83	0·94	1·29	−0·40	51·4	3·21	1·97	1·33	−0·09	61·4	33·3	26·5	4·02	+6·6	79·6	16·4		
2	9,320	900	3,660	86·8				1·74	0·78	1·24	−0·27	44·8	3·00	1·54	1·24	+0·44	51·3	31·5	22·3	5·15	+7·4	70·8	16·4		
2	9,320	900	4,345					1·75	0·82	2·47	−0·30	46·9	3·07	1·75	2·04	+0·30	57·1	32·7	22·7			69·4	15·8		

1 On experimental diet for two days—specimens not saved.
2 As the carmine did not appear within twenty-four hours for this period, the stools for the third and fourth periods were mixed, and half the results of analysis were credited to each period.

N.B.—Periods were of four days' duration, in this and succeeding protocols, unless otherwise stated.

Wgt. = Weight. Kilogrms. = Kilograms. Phosph'rus = Phosphorus. Per'd. = Period. Cals. = Calories. C.cm. = Cubic centimetres. Grms. = Grammes. Mgm. = Milligrammes.



GRAPH II.

Joan H., female, single, aged twenty-one. Diagnosis: normal control.

TABLE III.

Albert I., male, aged 38 years. Admitted to Metabolic Ward May 17, 1932. Discharged July 27, 1932. Diagnosis: Hyperthyreoidism.

Period Number.	Footnote Index.	Food Intake per Per'd. Cals.	Fluid Intake per Diem. C.cm.	Urine Volume per Per'd. C.cm.	Wgt. of Dried Feces. Grms.	Basal Metabolic Rate. %	Basal Pulse Rate.	Wgt. Kilogrms.	Calcium Metabolism per Period.					Phosphorus Metabolism per Period.					Nitrogen Metabolism per Period.					Blood Chemistry.	
									Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Excretion. Balance. Grms.	Ratio Urine to Intake. %	Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Excretion. Balance. Grms.	Ratio Urine to Intake. %	Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Excretion. Balance. Grms.	Ratio Urine to Intake. %	Ratio Stool to Intake. %	Calcium. Mgm. %	Inorganic Phosphorus. Mgm. %
0		16,330	1,750	6,815	141·8	+34·8	118	50·2	3·45	2·00	2·52	−1·07	58·0	5·08	4·86	1·28	−1·06	95·7	55·3	51·1	7·4	−3·2	92·4	13·4		
1		16,330	1,750	5,369	137·7	+44·0	118	50·0	3·22	2·00	2·75	−1·53	62·1	5·05	4·83	1·34	−1·12	96·2	54·6	50·7	7·0	−3·1	95·4	12·8		
2		16,330	1,750	6,203	154·0	+36·0	116	50·6	3·06	1·89	2·75	−1·58	61·8	5·11	5·10	1·37	−1·36	99·9	54·9	51·4	7·6	−4·1	93·6	13·9		
3		16,330	1,750	6,473	140·2	+36·5	108	50·8	3·06	1·81	2·82	−1·57	59·2	5·18	4·01	1·43	−0·27	77·4	58·5	40·9	7·4	+10·2	69·9	12·6		
4		16,330	1,750	6,480	135·6	+6·0	86	51·6	3·25	1·56	2·81	−1·12	48·0	5·62	3·22	1·60	+0·78	57·3	64·7	29·4	7·4	+27·9	45·4	11·4		
5		16,330	1,750	6,115	124·3	+9·3	84	53·1	3·25	1·17	2·54	−0·46	36·0	5·62	2·62	1·60	+1·35	46·9	57·9	24·8	7·1	+26·0	42·8	12·2		
6		16,330	1,750	5,665	117·2	+9·3	86	53·4	3·29	0·84	2·24	+0·21	25·5	5·74	2·66	1·49	+1·57	46·3	62·0	25·5	6·9	+29·6	41·1	11·1		
7		11,670	1,750	6,110	83·3	−12·0	80	53·0	2·34	1·01	1·36	−0·03	43·2	5·89	2·29	1·30	+0·2	58·9	40·2	23·9	5·5	+11·8	59·4	13·7		
8		11,670	1,750	7,390	87·3	−6·0	80	53·5	2·84	1·04	1·22	+0·58	36·6	5·00	2·92	1·24	+0·84	58·4	50·4	32·5	5·8	+12·2	64·5	11·4		
10	4	14,600	1,750																					

a Lugol's iodine, 3 cubic centimetres daily. Commenced on first day of period, and continued for four periods.

1 On an increasing diet for first three days, and then on 4,080 calories *per diem* for two days, during which the specimens were not saved.

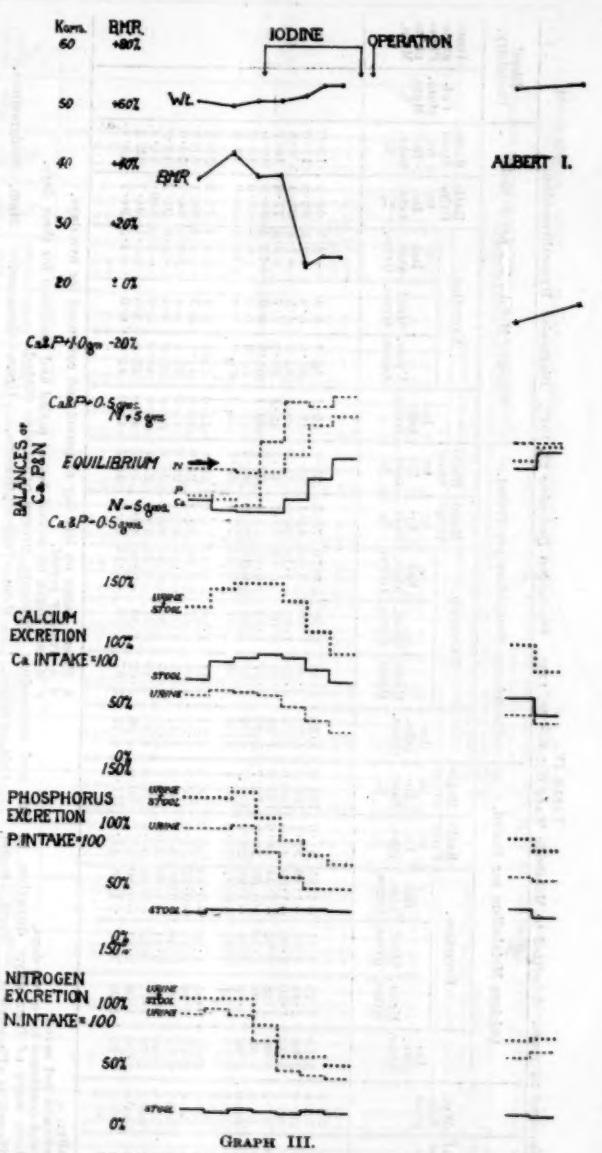
2 Subtotal thyroidectomy performed two days after the cessation of this period.

3 Twenty-three days after operation experimental diet began and continued for four days, during which specimens were not saved.

4 A five-day period.

N.B.—Periods were of four days' duration, in this and succeeding protocols, unless otherwise stated.

Wgt. = Weight. Kilogrms. = Kilograms. Phosph'us = Phosphorus. Per'd. = Period. Cals. = Calories. C.cm. = Cubic centimetres. Grms. = Grammes. Mgm. = Milligrammes.



GRAPH III.

Albert I., male, aged thirty-eight. Diagnosis: hyperthyreoidism.

Calcium balance: There was a lag of a whole period, and thereafter the balance became progressively less negative to become slightly positive (0·05 gramme *per diem*) during the fourth iodine period.

Metabolism After Operation.—After operation he remained in positive calcium, phosphorus and nitrogen balance on five-sevenths of the caloric intake of the pre-operation period.

In this patient the decreased production of thyroxin following the administration of iodine was associated with a marked improvement in calcium, phosphorus and nitrogen balance. Taken by themselves the results would indicate that the increased production of thyroxin had been the direct cause of the initial negative calcium and phosphorus balance, as Aub *et alii* and Hunter maintain.

TABLE IV.

Dorothy E., female, single, aged 22 years. Admitted to Metabolic Ward October 20, 1932. Discharged December 23, 1932. Diagnosis: Hyperthyreoidism.

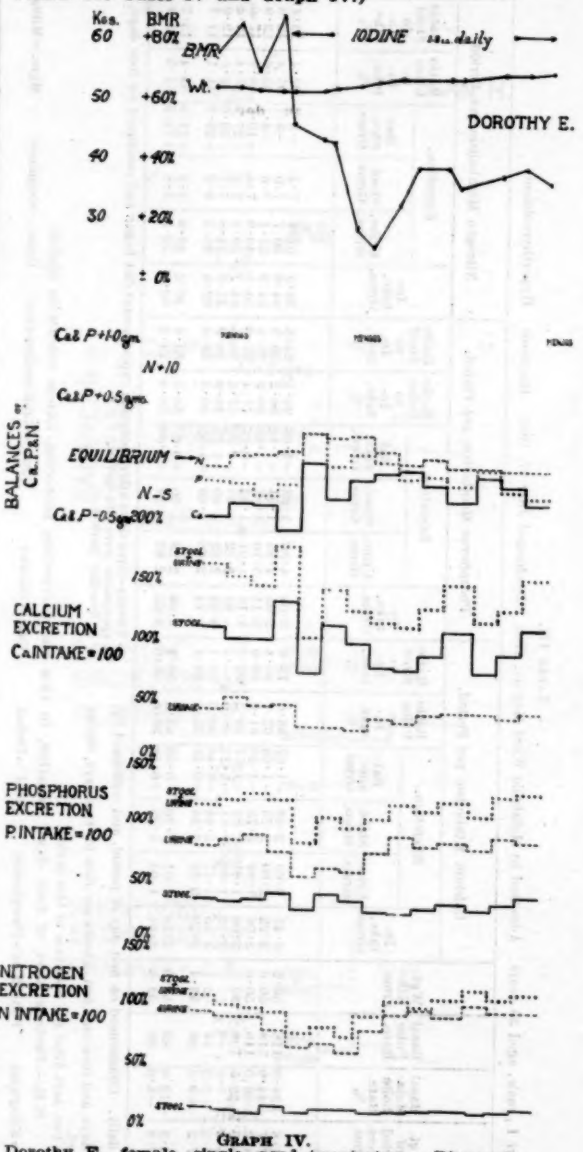
Period Number.	Footnote Index.	Food Intake per Per'd. Cals.	Fluid Intake per Diem. C.cm.	Urine Volume per Per'd. C.cm.	Wgt. of Dried Feces. Grms.	Basal Metabolic Rate. %	Basal Pulse Rate.	Wgt. Kilograms.	Calcium Metabolism per Period.					Phosphorus Metabolism per Period.					Nitrogen Metabolism per Period.					Blood Chemistry.	
									Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Excretion. Balance. Grms.	Ratio Urine to Intake. %	Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Excretion. Balance. Grms.	Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Excretion. Balance. Grms.	Ratio Urine to Intake. %	Ratio Stool to Intake. %	Calcium. Mgm. %	Inorganic Phosphorus. Mgm. %
0	a	7,000	1,800	129·5		+75·0	104	52·0	3·15	1·29	3·81	−1·95	41·0	121·0	4·92	3·86	1·76	−0·70	78·5	35·8	49·1	45·4	6·4	−2·7	92·5	13·0		
1		14,000	1,800	90·0		+85·0	106	52·0	2·84	1·48	2·85	−1·49	52·1	100·0	4·73	3·98	1·59	−0·84	84·1	33·6	49·1	43·6	5·4	+0·1	88·8	11·0		
2		14,000	1,800	123·8		+69·0	120	51·5	3·30	1·50	3·30	−1·50	45·5	132·0	4·79	4·29	1·69	−1·19	89·6	36·3	49·1	42·9	4·3	−1·9	87·4	8·8		
3		14,000	1,800	140·5		+52·0	112	51·5	2·96	1·38	3·92	−2·34	46·6	72·7	4·94	3·74	2·06	−0·96	75·7	41·7	49·1	38·3	7·7	+12·2	77·8	15·7		
4	1	14,000	1,800	86·1		+47·0	80	51·0	3·35	1·06	3·58	−0·09	29·9	114·0	4·74	2·77	1·43	+0·54	54·1	27·9	49·1	31·8	4·9	+12·4	64·8	10·0		
5	1	14,000	1,800	112·9		+46·0	84	52·0	3·35	0·88	3·34	−1·25	29·9	114·0	4·74	2·98	1·97	+0·21	62·9	41·6	49·1	32·9	6·4	+9·8	67·0	13·0		
6	1	14,000	1,800	104·2		+17·0	80	52·3	2·94	0·65	2·67	−0·67	25·4	99·6	4·38	2·60	1·57	+0·21	59·4	35·8	49·1	27·0	5·8	+12·2	60·0	13·0		
7		12,880	1,800	84·0		+11·0	84	52·0	2·68	0·68	2·67	−0·67	25·4	99·6	4·38	2·60	1·57	+0·21	59·4	35·8	45·0	27·0	5·8	+12·2	60·0	13·0		
8	1c	12,880	1,800	88·4		+25·0	92	52·0	2·51	0·91	1·98	−0·38	36·3	78·9	4·51	3·41	1·20	−0·10	75·6	26·6	45·0	35·5	5·1	+4·4	78·9	11·3		
9		12,880	1,800	105·3		+38·0	108	53·6	2·77	0·96	2·13	−0·32	34·6	76·9	4·52	4·03	1·17	−0·68	89·2	25·9	45·0	41·1	5·3	−1·4	91·1	11·8		
10		16,040	1,800	142·0		+31·0	106	53·7	2·77	1·12	2·46	−0·83	40·4	89·5	4·47	3·65	1·33	−0·51	81·7	29·8	45·0	39·0	5·4	+0·6	96·7	12·0		
11	1d	12,880	1,800	87·5		+35·0	102	53·8	3·40	1·38	3·71	−1·69	40·6	109·1	5·35	4·45	1·85	−0·95	83·2	34·6	45·0	52·0	7·9	−2·9	91·2	13·9		
12	1	12,880	1,800	98·3		+38·0	120	54·5	2·79	1·13	2·12	−0·46	40·5	75·9	4·37	3·49	1·21	−0·23	79·9	27·7	45·0	45·0	5·0	−5·0	100·0	11·4		
13	1e	12,880	1,800	121·3		+33·0	116	55·0	2·90	1·09	2·61	−0·80	37·7	90·0	4·06	3·62	1·39	−0·95	89·2	34·2	45·0	42·6	5·5	−3·1	94·7	12·2		
14						+33·0	120	54·2	2·60	1·08	2·90	−1·38	41·6	111·5	4·27	3·67	1·72	−1·12	86·9	40·3	45·0	42·6	6·9	−4·5	94·7	15·3		

1 Lugol's iodine, 1·8 cubic centimetres daily.
a On experimental diet for two days—specimens not saved.
b Menses began on second day of period and continued for seven days.
c Menses began on last day of period and continued for five days.
d A five-day period.
e Menses began on second day of period and continued for three days.

N.B.—Periods were of four days' duration, in this and succeeding protocols, unless otherwise stated.

Wgt. = Weight. Kilograms. = Kilograms. Phosph'us = Phosphorus. Per'd. = Period. Cals. = Calories. C.cm. = Cubic centimetres. Grms. = Grammes. Mgm. = Milligrammes.

CASE II.—Dorothy E. was aged twenty-two, a female, single. (For history see case report.) The estimated caloric requirement (basal × 4/5) = 3,670 *per diem*. The actual caloric intake was 3,500 *per diem*. The fluid intake was 1,800 cubic centimetres *per diem*. (For experimental details see Table IV and Graph IV.)



GRAPH IV.

Dorothy E., female, single, aged twenty-two. Diagnosis: hyperthyreoidism.

Fore-period.—Three four-day periods, rest in bed; no medication.

Iodine Therapy.—Eleven periods, all of four days, except the eighth, which was of five days; 1·8 cubic centimetres of Lugol's iodine were administered daily.

The object of study was to follow the calcium and phosphorus balance during and after the time that iodine was exerting its "typical" effect. It is well known that if iodine is continued after the basal metabolic rate curve has reached a low level, the metabolism frequently rises again, and the signs and symptoms of hyperthyreoidism become once more accentuated.

Metabolism During Fore-Period.—Basal metabolism varied between +70% and +88%, and showed no tendency to fall. The weight was practically constant.

The nitrogen balance was just in equilibrium.

The phosphorus balance was definitely negative, average −0·227 gramme *per diem*; range −0·175 to −0·268 gramme *per diem*.

The calcium balance was definitely negative, average −0·412 gramme *per diem*; range −0·37 to −0·488 gramme *per diem*.

Metabolism During Iodine Therapy.—Basal metabolism showed an immediate response, falling from +88% to +53% in three days, and continued to fall, reaching a minimum of +11% by the seventeenth day. It then began to rise again; by the twenty-fourth day it was +36%, at which level it remained constant till the study terminated.

Weight slowly but steadily increased throughout the whole time iodine was administered, and this in spite of a negative nitrogen balance during the last four periods. This phenomenon was noted in several patients.

Nitrogen balance became immediately positive, and nitrogen retention continued at an increased rate during the first three periods and then corresponding to the rising metabolism it began to fall, becoming slightly negative by the time the basal metabolism had reached its peak. The balance then remained slightly negative (−1·0 gramme approximately *per diem*).

Phosphorus balance did not show the immediate change noticed in the case of Albert I., and this was due to the very large stool weight of the first iodine period. Indeed, during iodine administration the stool weight varied greatly from period to period, although there was no constipation and although the carmine separated the stool with accuracy. During the second period the phosphorus balance became positive (the stool weight for the period was small), during the third period negative, during the fourth period positive and then increasingly negative in spite of a constant basal metabolic rate.

Calcium Balance.—During the first period the negative calcium balance was accentuated, owing to the large stool weight; during the second period equilibrium was almost reached; a negative balance obtained for the next two periods, and then equilibrium again for two periods (a period later than the phosphorus). The balance then became increasingly negative, in spite of a constant basal metabolic rate.

In this patient the evidence of a direct effect of thyroxin on calcium and phosphorus metabolism is not as definite as in Albert I., because towards the end of the experiment we have a progressively increasing loss of calcium and phosphorus at a time when the basal metabolism was constant.

TABLE V.

Darcia T., female, single, aged 21 years. Admitted to Metabolic Ward September 7, 1931. Discharged December 10, 1931. Diagnosis: Hyperthyroidism.

Period Number.	Footnote Index.	Light of Period. Days.	Food Intake per Period. Cals.	Fluid Intake per Diem. C.cm.	Urine Volume per Period. C.cm.	Basal Metabolic Rate. %	Basal Pulse Rate.	Wgt. Kilogrms.	Calcium Metabolism per Period.					Phosphorus Metabolism per Period.					Nitrogen Metabolism per Period.					Blood Chemistry.	
									Intake. Grms.	Excretion.				Intake. Grms.	Excretion.				Intake. Grms.	Excretion.				Calcium. Mgm. %	Inorganic Phosphorus. Mgm. %
										Urine. Grms.	Stool. Grms.	Balance. Grms.	Ratio Urine to Intake. %		Urine. Grms.	Stool. Grms.	Balance. Grms.	Ratio Stool to Intake. %		Urine. Grms.	Stool. Grms.	Balance. Grms.	Ratio Urine to Intake. %	Ratio Stool to Intake. %		
0																									
1		3	10,500	1,000	4,329	+36·0	104	53·6	1·67	1·17	1·70	−1·20	71·1	100·2	3·62	2·86	1·00	−0·24	79·2	27·7	38·4	32·6	4·5	+1·1	84·9	11·7		
2		3	10,500	1,000	3,550	+34·0	100	53·7	1·99	1·42	1·92	−1·35	71·4	96·5	3·77	3·11	1·00	−0·34	82·5	29·5	37·1	32·5	4·3	+0·3	87·6	11·5		
		4	14,000	1,000	5,590				2·45	1·71	2·15	−1·40	69·8	87·7	4·90	4·37	1·11	−0·58	89·2	22·6	50·5	48·1	5·0	−2·6	95·3	9·9		
		3	9,800	1,000	4,740	+20·0	100	53·5	1·72	1·31	1·78	−1·38	76·3	103·5	3·44	3·18	0·92	−0·66	92·4	26·7	35·3	32·5	5·0	−2·8	92·0	13·0		
		3	9,550	1,000	3,580	+13·5	100	53·6	1·66	1·03	1·38	−0·75	62·0	83·1	3·34	2·81	0·81	−0·28	84·1	24·3	33·4	27·6	4·4	−1·2	82·6	13·1		
		3	9,100	1,000	3,730	−2·5	94	53·6	1·62	1·19	1·78	−1·35	73·5	109·6	3·38	2·40	0·95	+0·03	71·0	28·1	33·6	24·7	4·4	+4·5	73·5	13·1		
		3	8,400	1,000	4,025	+4·0	70	54·2	1·46	0·90	1·27	−0·72	61·6	86·9	3·05	2·24	0·72	+0·09	73·6	23·6	31·8	21·5	4·3	+7·7	67·6	9·4		
		3	8,400	1,000	3,500	+12·0	80	55·0	1·48	1·03	1·49	−1·05	69·6	100·7	3·17	2·10	0·86	+0·21	66·2	27·1	30·8	19·2	4·0	+7·6	62·3	12·0		
		3	9,550	1,000	5,215				1·64	1·00	1·71	−1·08	60·9	104·2	3·51	2·24	1·03	+0·24	63·8	29·3	32·8	21·8	4·0	+6·4	66·5	14·0		
		3	8,750	1,000	4,040	+3·0	88	55·0	1·51	0·78	1·53	−0·81	51·6	101·4	3·10	2·26	0·87	−0·03	72·8	28·1	31·5	22·1	3·8	+6·9	70·1	12·1		
		4	11,200	1,000	5,610	+8·4	92	55·5	1·65	0·79	1·97	−0·32	37·3	77·8	4·06	2·40	0·94	+0·72	60·5	23·1	41·1	24·9	4·3	+11·9	70·6	10·5		
		4	11,200	1,000	5,290	+6·0	90	56·1	1·52	0·83	1·88	−0·52	37·9	85·9	3·94	2·53	1·06	+0·04	71·8	26·9	40·5	28·9	4·3	+7·3	71·3	10·6		
		4	11,200	1,000	6,000	+9·0	88	56·6	2·11	0·82	1·91	−0·62	38·8	90·4	3·94	3·40	1·03	−0·48	86·3	26·1	39·2	35·6	4·5	−0·9	90·8	11·5		
14		4	11,200	1,000	6,370	+14·0	94	55·6	2·16	0·68	2·09	−0·60	31·5	96·7	3·92	3·42	1·06	−0·56	87·2	27·1	38·8	42·1	5·1	−8·4	108·5	13·1		
15		4	12,400	1,000	5,750	+26·5	108	55·3	2·20	0·66	1·56	−0·02	30·0	70·9	4·09	3·10	0·77	+0·20	75·8	18·8	41·4	43·6	3·5	−5·7	105·3	8·4		
16		4	12,600	1,000	4,950	+30·0	116	55·3	2·28	0·49	2·06	−0·28	21·7	91·2	4·02	2·85	0·97	+0·20	70·8	24·1	41·2	37·0	4·8	−0·6	89·8	11·6		
17		4	12,600	1,000	4,210	+30·0	120	55·6	2·43	0·35	1·67	−0·20	14·4	76·9	4·35	2·47	0·87	+1·01	56·8	20·2	44·4	34·4	5·0	+5·0	77·5	11·2		
18		4	12,600	1,000	3,490	+28·0	118	55·0	2·52	0·38	1·86	+0·32	14·8	72·7	4·38	2·58	0·84	+0·96	58·9	19·2	42·8	31·8	5·0	+6·0	74·3	11·6		
19		4	12,600	1,000	4,185	+34·6	118	55·0	2·52	0·41	1·83	+0·26	16·3	72·6	4·38	2·64	0·93	+0·81	60·3	21·2	43·3	35·1	4·5	+3·7	81·0	10·4		
20						+47·0	130																					
21		4	12,600	1,000	5,730	+43·0	118	55·6	2·72	0·46	2·01	+0·24	17·6	73·9	4·51	3·04	0·93	+0·54	67·4	20·6	45·2	36·0	3·5	+5·7	79·7	7·7		
22		5	15,750	1,000	5,300	+36·0	112	54·8	2·72	0·69	2·13	−0·13	25·4	78·3	4·67	3·97	0·94	−0·24	85·0	20·1	46·8	41·3	4·3	+1·2	88·2	9·2		
23		4	12,600	1,000	4,970	+28·0	112	53·6	2·55	0·64	2·10	−0·19	25·1	82·3	4·65	3·39	0·96	+0·28	72·9	21·1	45·3	36·8	4·9	+3·6	81·2	10·8		
24						+36·0	104																					
25	44	4	12,600	1,000	6,280	+28·0	104	53·5	2·37	0·71	1·62	+0·04	29·9	68·4	4·27	3·07	0·78	+0·42	71·9	18·3	44·4	33·7	3·7	+7·0	75·8	8·3		

a Lugol's iodine, 1·0 cubic centimetres daily during fourth period.
b Lugol's iodine, 2·0 cubic centimetres daily during periods five to eleven, inclusive.
c Exposure to superficial X ray on fourth day of fifteenth period.
d Exposure to superficial X ray on fourth day of twenty-first period.

1 On experimental diet for three days—specimens not saved.
2 Menses began on second day and continued for seven days, and were excessive.
3 Menses began on second day and continued for nine days, and were excessive.
4 Menses began on second day and continued for five days, and were associated with nausea and vomiting on the third day.

N.B.—Periods were of four days' duration, in this and succeeding protocols, unless otherwise stated.

Wgt. = Weight. Kilogrms. = Kilograms. Phosph'us = Phosphorus. Per'd. = Period. Cals. = Calories. C.cm. = Cubic centimetres. Grms. = Grammes. Mgm. = Milligrammes.

Patient Treated with Iodine Followed by X rays.—One patient was treated with iodine and then had X rays.

CASE III.—Darcia T. was a female, single, aged twenty-one. (For history see case report.) This was our first patient, and we attempted too much. We varied the diet with changes in the basal metabolism; we experimented with periods of three and four days' duration; we gave the iodine in increasing dosage, followed by a second rest period without iodine, then X ray therapy. We were still experimenting with chemical methods and were having a great deal of trouble with stools and food by using an acid digestion method,[Gauss] so that we could not keep up to date with our analyses. As changes in salt metabolism are slow and often delayed, it is important to attempt only one experiment on one patient if correct deductions are to be drawn.

The estimated caloric requirement (basal × 1·3) = 2,880 *per diem*. The actual caloric intake was 3,000 *per diem*. The fluid intake was 1,600 cubic centimetres *per diem*. The caloric intake was varied frequently according to the basal metabolic rate. (For experimental details see Table V and Graph V.)

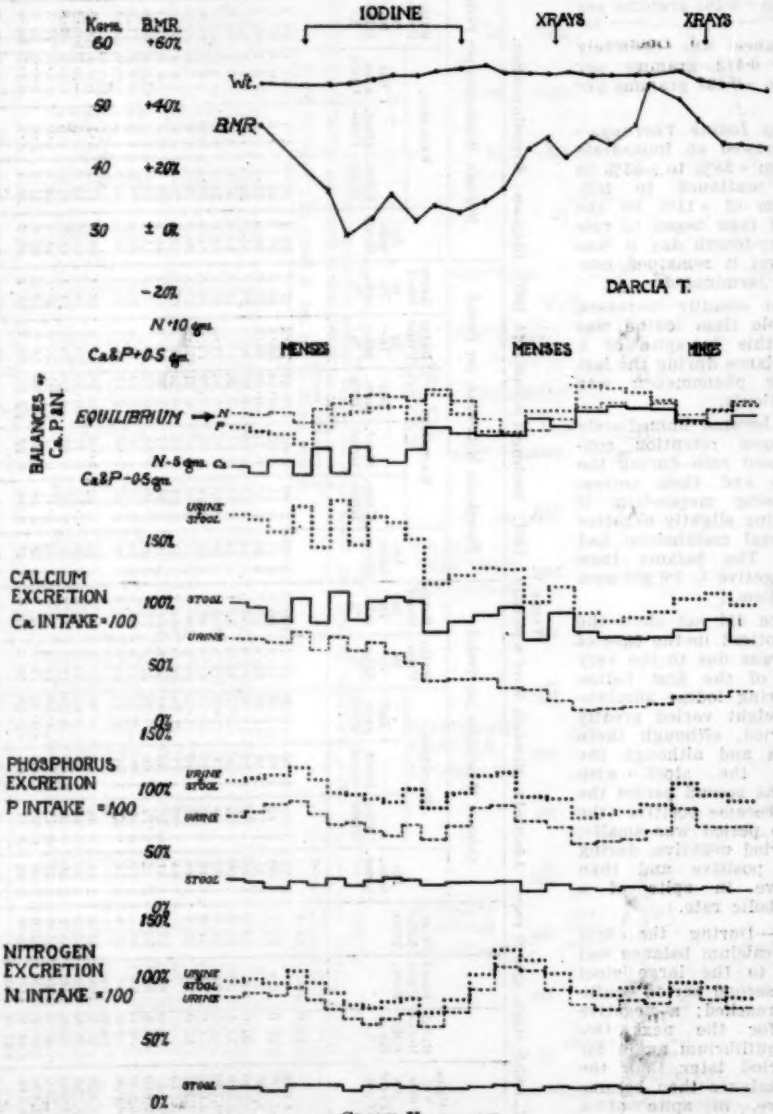
Fore-Period.—Ten days' duration—two three-day periods and one four-day period.

Iodine Therapy.—Seven three-day periods, then one four-day period. Lugol's iodine, 1·4 cubic centimetres, was given daily for four days, two cubic centimetres daily for the remaining time.

Rest-period.—Four four-day periods.

X Ray Therapy.—Two exposures[1] with an interval of twenty days; seven four-day periods and one five-day period. The patient was under observation for eighty-four consecutive days.

[1] Dose of X rays: Kilovolts, 140; milliampères, 3; filter, four millimetres aluminium; distance, 25 centimetres; time, five minutes to each lobe.



GRAPH V.

Darcia T., female, single, aged twenty-one. Diagnosis: hyperthyreoidism.

Metabolism During Fore-period.—The basal metabolism fell from +36% to +20%, the basal pulse rate remaining constant. The weight remained constant.

The nitrogen balance was slightly positive, average +0·4 gramme *per diem*.

The phosphorus balance was slightly negative, average −0·112 gramme *per diem*.

The calcium balance was definitely negative; average −0·4 gramme *per diem*.

Metabolism During Iodine Therapy.—Basal metabolism showed a typical response and fell to −2·5% by the eighth day, and then remained below +10% for the remainder of the time iodine was administered.

Weight increased steadily, although the diet was decreased as the basal metabolic rate fell.

Nitrogen balance continued positive at a constant level, definitely higher than during the fore-period, the average being +1·7 grammes *per diem*.

Phosphorus balance became positive during the third iodine period and remained positive except for a very slight negative balance in the seventh period.

Calcium balance showed marked fluctuations during the first four iodine periods, due very largely to changes in fæcal calcium (compare case Dorothy E.), and then progressively approached equilibrium, so that during the last iodine period the loss was only 0·08 gramme *per diem*.

Metabolism During Rest-Period.—It is difficult to decide whether the changes during this period were the result of the cessation of iodine therapy or the consequence of its administration. Basal metabolism progressively rose, and by the fourth period was +30%.

Weight was constant, but adjustments were made in the diet when the basal metabolic rate rose.

Nitrogen balance became negative during the second period and remained so for the remainder of the rest-period.

Phosphorus balance was positive for the first and last period, but definitely negative for the second and third;

TABLE VI.

Marjorie R., female, aged 12 years. Admitted to Metabolic Ward May 31, 1932. Discharged September 9, 1932. Diagnosis: Hyperthyreoidism.

Period Number.	Footnote Index.	Food Intake per Per'd. Cals.	Fluid Intake per Diem. C.cm.	Urine Volume per Per'd. C.cm.	Wgt. of Dried Faeces. Grms.	Cals. Per Sq. Metre. per Hour.	Basal Pulse Rate.	Wgt. Kilograms.	Calcium Metabolism per Period.					Phosphorus Metabolism per Period.					Nitrogen Metabolism per Period.					Blood Chemistry.	
									Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion.			Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Calcium. Mgm. %	Inorganic Phosph'us. Mgm. %
										Urine. Grms.	Stool. Grms.	Balance. Grms.				Urine. Grms.	Stool. Grms.	Balance. Grms.		Urine. Grms.	Stool. Grms.	Balance. Grms.			
I-IV		*Ad lib.*																						
1		11,670	1,050	4,551	83·3	49·8	126	31·3	2·21	1·80	2·21	−1·80	81·4	100·0	3·86	2·55	1·71	−0·40	66·1	44·3	40·4	28·3	4·3	+7·8	70·1	10·6		
2		11,670	1,050	5,090	82·8	49·2	126	31·7	2·16	2·41	2·28	−2·54	111·5	105·5	4·01	3·18	1·69	−0·86	79·3	42·2	43·7	35·7	5·0	+3·0	81·7	11·5		
3		11,670	1,050	4,558	82·7	49·2	120	31·7	2·31	2·31	2·47	−2·29	91·3	106·9	4·02	2·85	1·84	−0·67	70·9	45·8	44·1	35·3	4·3	+4·6	79·8	9·8		
4		11,670	1,050	4,590	73·1	49·6	116	31·4	2·22	2·22	2·30	−2·34	104·7	108·4	3·80	2·75	1·61	−0·56	72·3	42·3	39·4	33·4	4·0	+2·0	84·8	10·2		
5	a	11,670	1,050	4,355	77·9	49·2	126	31·7	2·20	2·16	2·33	−1·89	79·1	105·9	3·84	2·31	1·64	−0·11	60·2	42·7	40·9	29·1	4·7	+3·9	77·7	10·3		
6		11,670	1,050	4,150	86·3	45·6	122	32·2	2·16	1·74	2·38	−1·92	81·9	110·1	3·79	2·39	1·75	−0·35	63·1	46·2	38·6	30·0	4·8	+12·4	77·7	12·2		
7		11,670	1,050	4,700	86·3	50·4	124	32·0	2·14	1·70	2·50	−1·90	69·6	102·4	3·91	2·31	1·81	−0·21	59·1	45·8	40·9	28·3	4·8	+11·5	62·9	11·5		
8		11,670	1,050	4,750	83·3	52·3	120	33·0	2·14	1·74	2·44	−1·34	57·2	100·0	3·89	1·88	1·78	−0·23	48·3	45·8	40·2	25·3	3·4	+5·9	62·9	8·4		
9		11,670	1,050	3,685	85·8	46·8	116	33·4	1·97	1·42	2·44	−1·59	62·5	107·0	4·02	2·29	2·06	−0·33	57·0	51·3	43·2	32·4	4·9	+5·9	75·0	11·3		
10		11,670	1,050	4,575	83·2	50·4	120	33·6	2·06	0·90	2·14	−1·98	43·6	103·8	3·77	2·21	1·77	−0·21	58·6	47·0	39·7	28·7	4·8	+6·2	72·3	12·3		
11		11,670	1,050	5,180	93·3	47·4	108	34·6	2·08	0·55	2·27	−0·75	26·4	109·1	4·09	2·13	1·76	+0·20	52·1	43·0	40·6	26·4	5·8	+8·4	65·0	14·2		
12		11,670	1,050	5,090	91·3	45·6	108	34·6	2·13	0·60	2·05	−0·58	23·4	96·2	4·00	2·15	1·53	+0·32	53·7	38·2	41·0	27·3	5·9	+5·9	66·3	12·7		
13		11,670	1,050	4,870	89·3	45·6	116	35·0	2·22	0·97	2·00	−0·15	16·7	90·1	3·91	2·10	1·38	+0·42	53·7	35·6	41·5	26·4	5·3	+11·2	60·9	12·7		
14		12,830	1,050	5,095	101·5	46·2	116	35·2	2·44	0·96	2·02	−0·13	12·8	82·8	4·58	2·18	1·38	+1·02	47·6	30·1	46·0	27·8	5·7	+11·6	61·7	12·3		
15		12,830	1,050	5,730	83·5	52·4	120	35·4	2·30	1·26	1·95	+0·09	11·3	84·7	4·48	2·25	1·30	+0·93	50·2	29·0	51·3	27·8	5·0	+18·5	54·3	19·7		
16		12,830	1,050	5,460	79·8	50·4	120	35·8	2·40	0·72	1·67	+0·54	7·7	69·5	4·36	2·24	1·24	+0·88	51·3	28·4	46·0	29·1	4·6	+12·3	63·2	10·0		
17		12,830	1,050	5,240	85·4	46·8	120	36·8	2·50	0·12	1·38	+1·00	4·8	55·2	4·32	2·07	1·18	+1·07	47·9	27·3	43·7	28·5	5·0	+10·2	65·2	11·4		
18	c	12,830	1,050	5,390	73·7	46·2	116	37·2	2·46	0·06	0·94	+1·46	2·45	36·2	4·35	1·96	0·80	+1·59	45·1	18·4	44·0	23·4	4·4	+16·2	53·1	10·0		
19		12,830	1,050	4,980	84·0	46·8	108	38·1	2·46	0·05	0·77	+1·63	2·04	31·0	4·41	1·77	0·66	+1·78	40·2	19·5	44·6	21·4	5·6	+17·6	47·9	12·6		
20		12,830	1,050	4,810	74·8	45·6	100	38·6	2·30	0·04	0·56	+1·70	1·82	25·6	4·24	1·54	0·81	+1·80	36·3	19·1	45·1	18·3	4·7	+22·1	40·6	10·0		

a Exposure to superficial X ray on third day of period.
b Exposure to superficial X ray on first day of period.
c Lugol's iodine, 2·0 cubic centimetres daily, beginning on first day of period and continuing for three periods.

1 On experimental diet for sixteen days, but specimens not kept. See case report.
2 Two days after cessation of experimental study, but still on iodine.

N.B.—Periods were of four days' duration, in this and succeeding protocols, unless otherwise stated.

Wgt. = Weight. Kilogrms. = Kilograms. Phosph'us = Phosphorus. Per'd = Period. Cals. = Calories. C.cm. = Cubic centimetres. Grms. = Grammes. Mgm. = Milligrammes.

however, these two periods coincided with the menstrual cycle, and in this patient menstruation seemed to determine an increased phosphorus excretion.

Calcium balance continued to approach equilibrium, in spite of a rising metabolism, and for the last period the loss was only 0·005 gramme *per diem*.

Metabolism During X Ray Therapy.—Basal metabolism continued its upward trend and reached a maximum of +47·3% during the fourth X ray period; it then gradually fell to a level of +28%, which was reached during the seventh X ray period.

Weight remained constant till the last three periods, when, in spite of a positive nitrogen balance, a constant diet and a falling basal metabolic rate, there was a loss of two kilograms in sixteen days. In this case the weight varied independently of the nitrogen retention, but in an opposite direction to case Dorothy E.

Nitrogen balance was positive throughout the whole of the X ray period.

Phosphorus balance was positive for every period except the one that was coincident with menstruation, when it became slightly negative.

Calcium balance became positive during the second period after the first dose of X rays, and the storage of calcium proceeded at a constant rate during the next four periods, in spite of a rising metabolism; then it fell toward equilibrium during the remaining four periods, though the metabolism was falling.

The complex nature of the experiment in this patient makes it impossible to decide the part different therapeutic agents had in bringing about a positive calcium and phosphorus balance; but the results indicate quite definitely that the activity of the thyreoid gland *per se* played no part, as the changes in calcium and phosphorus metabolism were often opposite in sense to the changes in general metabolism.

Patients Treated with X Rays.—Four patients were treated with X rays.

CASE I.—Marjorie R. was a female aged twelve. (For history see case report.) The fore-period was very long, thirty-two days, but the data for the first sixteen days are not very reliable; the patient was in a general ward, had access to food and fluid during the night, and for the first three periods had intractable nocturnal enuresis. On the seventeenth day she was transferred to the special ward, it was made impossible for her to get any food other than what was allowed, and by curtailing the fluid intake to 1,050 cubic centimetres daily and stopping all fluid after 4 p.m. we had no further trouble with enuresis; she became an ideal experimental subject and was under observation for ninety-six consecutive days.

The estimated caloric requirement (basal × 3/2) = 2,440. (For experimental details see Table VI and Graph VI.) The caloric intake was 2,900 for seventeen periods, 3,200 for the last seven periods. As she was a growing child, we allowed her a growth quota of 500 calories *per diem*. This large quantity of food was taken readily.

Fore-period (excluding first sixteen days).—Four four-day periods, rest in bed, no medication.

X Ray Therapy.—Two exposures to superficial X rays[1] were made, the first at the beginning of the fifth period, the second thirty days later.

Iodine Therapy.—Three four-day periods, at end of experiment. Lugol's iodine, two cubic centimetres, was given daily.

Metabolism During Fore-Period.— Basal metabolism was practically constant for the whole thirty-two days, range 49·2 to 52·2 calories per square metre per hour. (See discussion in appendix on analytical methods for reason for thus expressing the heat production.) The basal pulse rate was also constant. It is extraordinary how little effect rest in bed without medication has in some cases of hyperthyreoidism. Tibbetts, McLean and Aub[(124)] also remark on this.

Weight increased slowly but steadily.

Nitrogen balance was definitely positive; average gain 1·1 grammes *per diem*.

Phosphorus balance was moderately negative; average −0·156 gramme *per diem*.

Calcium balance was severely negative; average −0·561 gramme *per diem*.

Metabolism During X Ray Therapy.— Basal metabolism showed minor variations, which were apparently due to a varying effect of radiation on different parts of the thyreoid gland. There was a slight tendency for the metabolism to fall, but taking into consideration the basal metabolism, the pulse rate, the general clinical condition and the state of the thyreoid gland itself, no appreciable effect on the hyperthyreoidic state was induced by the first two doses of X rays. This is borne out by the definite response to iodine at the end of the experimental study, and more forcibly by the subsequent history of the patient; after the termination of the study the hyperthyreoidism became more marked. (See case report.)

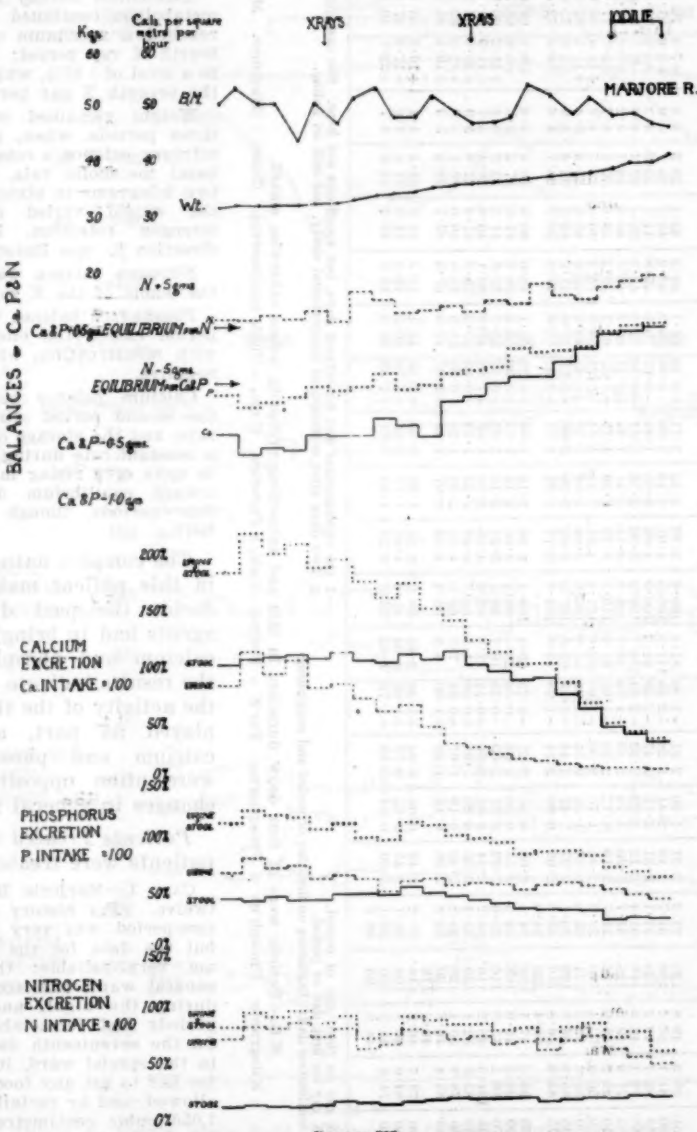
Weight continued to increase steadily, but the rate of gain was only influenced by the increase in diet beginning at the eighteenth period, and was uninfluenced by X ray therapy.

Nitrogen balance was practically uninfluenced by the X rays, but became definitely more positive when the diet was increased, and decidedly more positive when iodine therapy was instituted.

Phosphorus balance was very early influenced by the X rays, and even during the first period equilibrium was practically established, to remain so till the seventh X ray period; then the balance became positive and storage of phosphorus proceeded at an ever-increasing rate. The earliest change was in the urine; beginning during the first period, the excretion of phosphorus in the urine fell progressively throughout the experiment. The output in the fæces was not influenced till the sixth X ray period; then it fell progressively throughout the experiment.

Calcium balance was influenced during the first period. The loss of calcium gradually diminished, the balance finally becoming positive during the third period after the second X ray treatment; calcium storage proceeded at an increasing rate and overtook the phosphorus storage during the sixth period after the second X ray treatment.

Metabolism During Iodine Therapy.— The basal metabolism fell to 44·6 calories per square metre per hour, the pulse rate fell twenty beats per minute. The weight increased at a more rapid rate. The positive nitrogen balance became very large, and the retention of phosphorus and calcium became greatly augmented. The output of phosphorus and calcium fell in both urine and stool.



GRAPH VI.

Marjorie R., female, aged twelve. Diagnosis: hyperthyreoidism.

The storage of calcium, towards the end of the experiment, demonstrates the ability of the body to retain and utilize calcium once the pathological condition which determined the calcium loss had ceased to operate. Sherman and Hawley[(104)] found that female children aged ten to fourteen years, on a calcium intake in the vicinity of 1·0 gramme *per*

[1] The X ray dosage was the same as for Darcia T.

diem, chiefly from milk, stored calcium at the rate of 0·01 gramme per kilogram daily; when the calcium was derived partly from milk and partly from vegetables the storage was not so good. This patient, on an intake of 0·5 gramme calcium *per diem*, derived partly from milk but chiefly from vegetables, stored 0·011 gramme calcium per kilogram *per diem*. (Average of periods 18, 19, 20.)

The change from a gross negative calcium balance to a definite positive balance was brought about by the application of two doses of therapeutic X rays to the neck. The hyperthyreoidic state both clinically and as estimated by the basal heat production remained practically uninfluenced during this profound change in calcium and phosphorus metabolism, so that the X rays must have had an effect on glandular tissue other than the thyreoid gland. It seems logical to conclude that the parathyreoid glands had been hyperactive and that the X rays reduced their secretory activity.

The subsequent administration of iodine led to a definite decrease in thyreoid activity, the heat production falling and the clinical condition improving. The calcium and phosphorus balances became more markedly positive, but this is an indirect effect of iodine, and most probably results as follows: (i) The decrease in circulating thyroxin is followed by a general lowering of the rate of cell metabolism, in which the parathyreoid apparatus shares; (ii) the vascularity of the thyreoid gland diminishes and this also means a diminished blood supply to the parathyreoid glands.

CASE II.—Phyllis W. was a female, aged twenty. (For history see case report.) The estimated caloric requirement (basal × 1·3) = 3,200 *per diem*. The caloric intake was 2,920 for first ten periods, 3,210 for last nine periods. The fluid intake was 1,500 cubic centimetres *per diem*. (For experimental details see Table VII and Graph VII.)

Fore-Period.—Three four-day periods. The first exposure to superficial X ray was given on the third day of the third period.

X Ray Therapy.—Three superficial X ray exposures were given.[1] The first application was on the eleventh day of the experimental study, the second on the thirty-second day, the third on the fifty-seventh day. This patient was under observation for seventy-six consecutive days.

Metabolism During Fore-Period.—Basal metabolism fell steadily from +50% to +30%. The basal pulse rate fell from 126 to 110 per minute.

Weight fell from 56 kilograms to 55·2 kilograms in the twelve days.

Nitrogen balance was slightly negative, −1·0 gramme *per diem* approximately.

Phosphorus balance was slightly negative, −0·17 gramme *per diem* approximately.

Calcium balance was moderately negative, −0·24 gramme *per diem* approximately.

[1] X ray dosage was the same as for Darcia T.

TABLE VII.

Phyllis W., female, single, aged 20 years. Admitted to Metabolic Ward January 5, 1933. Discharged March 30, 1933. Diagnosis: Hyperthyreoidism.

Period Number.	Footnote Index.	Food Intake per Per'd. Cals.	Fluid Intake *per Diem*. C.cm.	Urine Volume per Per'd. C.cm.	Wgt. of Dried Feces. Grms.	Basal Metabolic Rate. %	Basal Pulse Rate.	Wgt. Kilogrms.	Calcium Metabolism per Period.					Phosphorus Metabolism per Period.					Nitrogen Metabolism per Period.						Blood Chemistry.	
									Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Calcium. Mgm. %	Inorganic Phosphorus. Mgm. %
										Urine. Grms.	Stool. Grms.	Balance. Grms.				Urine. Grms.	Stool. Grms.	Balance. Grms.				Urine. Grms.	Stool. Grms.	Balance. Grms.				
0																											
1	1	14,600	1,500	4,380	80·0	+50·0	126	55·9																			
2		11,670	1,500			+49·0	120	56·0																			
3						+42·0	116	56·2	2·57	1·35	1·79	−0·57	52·5	69·7	4·13	3·18	1·85	−0·40	77·0	32·7	40·9	37·8	5·0	−1·9	92·4	12·2		
4		11,670	1,500	5,360	66·5	+31·0	110	55·2	2·74	1·61	1·79	−0·66	58·8	65·3	4·28	3·33	1·84	−0·09	77·8	24·3	44·5	37·7	2·5	+2·3	84·7	5·6	11·4	4·1
5		11,670	1,500	6,620	99·5	+30·1	112	55·2	2·31	1·8	2·11	−1·69	77·9	91·4	3·49	2·68	1·51	−1·46	98·7	41·0	44·5	37·7	2·5	+2·3	84·7	5·6		
6		11,670	1,500	6,240	92·0	+30·9	100	55·3	2·33	1·97	1·99	−1·63	84·5	85·4	4·07	3·78	1·49	−1·20	92·9	36·6	40·9	39·9	5·4	+8·0	107·0	14·5		
7		11,670	1,500	6,040	80·7	+30·0	110	55·1	2·37	2·04	2·38	−2·05	86·1	100·4	4·03	3·53	1·61	−0·91	89·2	39·9	40·9	40·2	5·5	+4·8	98·3	13·5		
8		11,670	1,500	7,840	109·0	+31·0	96	55·5	2·47	1·91	2·53	−1·97	77·3	102·4	4·01	3·35	1·62	−0·96	83·5	40·4	40·9	38·2	5·1	+2·4	93·4	12·5		
9		11,670	1,500	6,280	80·3	+30·0	116	55·5	2·22	1·84	2·13	−1·75	82·8	96·0	4·11	3·54	1·63	−0·67	86·1	34·6	40·9	36·8	5·0	+0·9	90·0	12·3		
10	4b	11,670	1,500	4,500	91·0	+44·0	112	55·5	2·54	1·95	2·30	−1·76	76·8	90·5	3·95	3·54	1·50	−0·60	92·7	33·2	40·9	37·1	4·9	−1·1	90·7	12·0		
11		11,670	1,500	4,920	75·4	+36·0	124	55·5	2·18	1·63	1·92	−1·37	74·8	88·1	3·95	3·17	1·31	−0·54	82·0	33·2	40·9	37·1	4·9	−1·1	90·7	12·0		
12		11,670	1,500	5,220	90·0	+22·0	126	55·5	2·20	1·50	2·11	−1·41	68·2	95·9	4·03	3·47	1·47	−0·61	78·7	36·5	40·9	31·3	6·1	−3·5	76·5	14·9		
13		12,830	1,500	5,840	81·3	+29·0	120	55·0	2·57	1·51	1·93	−0·87	58·8	75·0	4·35	3·02	1·57	−0·04	69·4	31·5	45·0	39·7	5·2	−0·1	88·2	13·4		
14		12,830	1,500	4,820	96·5	+24·0	104	55·5	2·80	1·45	2·60	−1·25	51·8	92·9	4·27	3·57	1·60	−0·90	58·9	37·5	45·0	37·0	6·0	−2·0	82·2	13·8		
15		12,830	1,500	6,330	99·0	+29·0	118	56·0	2·94	1·50	2·83	−1·39	51·0	96·3	4·46	3·95	1·60	−0·49	72·8	40·4	45·0	37·5	6·2	−1·4	89·3	13·8		
16		12,830	1,500	7,190	94·0	+27·0	112	56·0	2·76	1·45	2·25	−0·94	52·5	81·6	4·37	3·57	1·45	−0·65	71·7	33·2	45·0	40·2	5·8	−1·4	91·6	12·9		
17		12,830	1,500	7,230	89·0	+30·0	104	56·1	2·43	1·24	2·03	−0·84	51·0	83·6	4·31	3·14	1·63	−0·56	72·8	33·2	45·0	37·9	5·9	−1·2	84·2	13·1		
18		12,830	1,500	7,140	100·0	+25·0	116	56·4	2·68	1·30	2·42	−1·04	48·5	90·1	4·18	3·14	1·45	−0·59	73·1	33·2	45·0	39·8	6·3	−1·0	88·4	13·8		
19		12,830	1,500	5,060	93·5	+23·0	116	56·8	2·66	1·50	2·31	−1·25	58·6	90·1	4·45	3·98	1·55	−0·98	65·1	34·8	45·0	34·5	5·2	−4·7	76·7	12·9		
		12,830	1,500	5,770	94·5	+22·0	116	56·9	2·44	0·77	1·88	−0·23	31·6	77·0	4·21	3·00	1·23	−0·02	71·0	34·8	45·0	30·4	5·7	−2·9	69·9	13·0		
		12,830	1,500	5,560	86·5	+27·0	100	57·0	2·69	1·21	2·07	−0·67	45·0	76·9	4·24	3·48	1·32	−0·56	82·1	31·1	45·0	39·9	5·4	−0·3	88·7	12·0		

a First exposure to superficial X ray on third day of period.
b Second exposure to superficial X ray on fourth day of period.
c Third exposure to superficial X ray on first day of period.
1 On experimental diet for five days—specimens not saved.
2 One specimen of stool (approximately one-eighth of whole period) was lost.
3 Menses began on last day and continued for four days.
4 Menses began on second day and continued for four days.
5 Menses began on third day and continued for four days.

N.B.—Periods were of four days' duration, in this and succeeding protocols, unless otherwise stated.

Wgt. = Weight. Kilogrms. = Kilogrammes. Phosph'us = Phosphorus. Per'd. = Period. Cals. = Calories. C.cm. = Cubic centimetres. Grms. = Grammes. Mgm. = Milligrammes.

The results cannot be given accurately for the fore-period, as one specimen of stool, representing about one-eighth of the total fæces for the second period, was lost.

Metabolism During X Ray Therapy.—Basal metabolism remained in the vicinity of +30% between the first and second applications of X rays, with a tendency to rise before the second application. From the second dose of X rays to the end of the study the basal metabolism fluctuated between +20% and +30%, tending to remain on the whole in the vicinity of +30%. The basal pulse rate fluctuated between 96 and 126 per minute, without any correlation to the basal metabolic rate. The ward pulse chart was very irregular and the pulse was often soft. On the whole, the three exposures to X rays had very little effect on heat production during the period of experimental study.

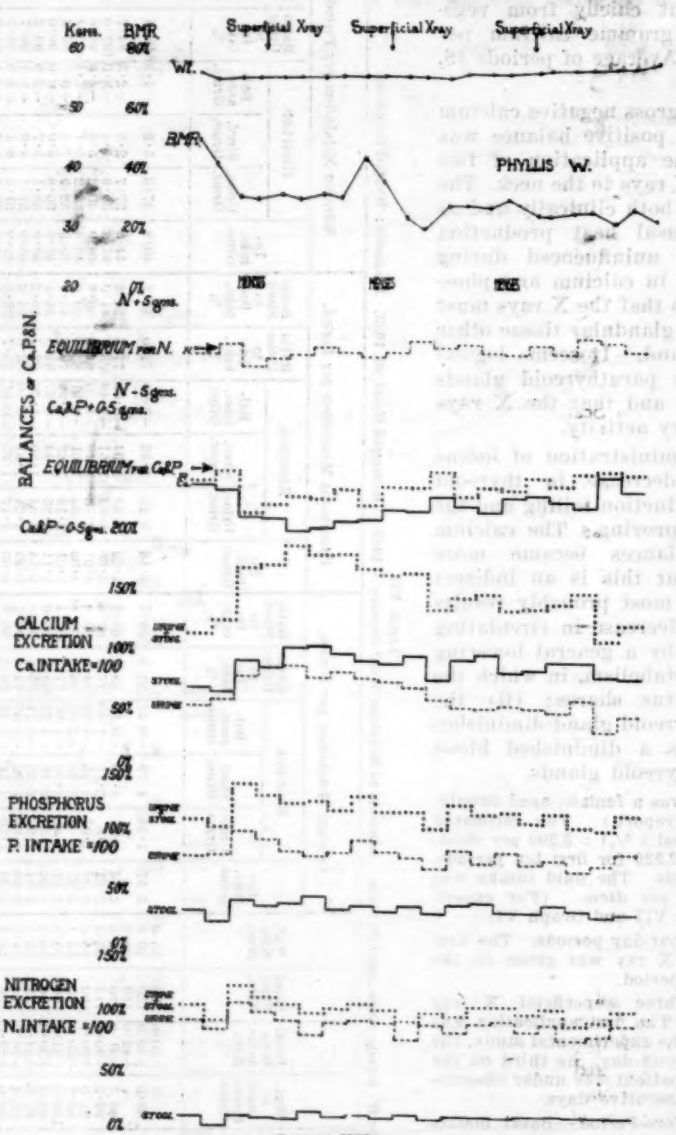
Weight remained constant at 55·5 kilograms, till the diet was increased in the ninth X ray period, and thereafter it increased very slowly but steadily to reach 57·7 kilograms at the end of the study.

Nitrogen balance fluctuated between slightly positive and slightly negative throughout, and was uninfluenced by an increase of 1·0 gramme nitrogen *per diem* in the diet.

Phosphorus balance: The negative phosphorus balance increased in the five periods following the first exposure to X rays to an average of −0·249 gramme *per diem*. Following the second and third exposures to X rays the balance approached equilibrium; average of six periods following second exposure −0·141 gramme *per diem*; average of five periods following the third exposure −0·074 gramme *per diem*. As the basal metabolism was practically constant throughout the X ray therapy the changes in the phosphorus balance were independent of the activity of the thyreoid gland.

Calcium balance: The negative calcium balance increased almost 100% following the first dose of X rays, the average negative daily balance for the five periods being 0·456 gramme. Following the second and third doses of X rays the negative balance became progressively smaller, the average negative daily balance for the six periods following the second exposure being 0·301 gramme and the average negative daily balance for the five periods following the third exposure being 0·202 gramme. The rise and fall in calcium loss was quite independent of the basal metabolism.

On the whole this patient was very disappointing from an experimental point of view, as we were unable to obtain any important changes in the metabolism of calcium and phosphorus. However, the results provide evidence that the loss of calcium in hyperthyreoidism is not in all cases "out of all proportion to the basal metabolism". This patient was only in slight negative balance in the fore-period at a time when the basal metabolism was between +42% and +50%. The results also indicate that the parathyreoid apparatus may be stimulated before being depressed by X ray therapy, and taken with the results of other cases, provide a warning that a series of cases must be carefully and fully studied before adequate conclusions can be drawn.



GRAPH VII.

Phyllis W., female, single, aged twenty. Diagnosis: hyperthyreoidism.

CASE III.—Dulcie S. was a female aged seventeen, married. (For history see case report.) The estimated caloric requirement (basal × 5/4) = 2,570 *per diem*. The caloric intake was 2,570 for the first four periods, 2,920 for the next four periods, 3,210 till the end of the experiment. The fluid intake was 1,600 cubic centimetres *per diem*. (For experimental details see Table VIII and Graph VIII.)

Fore-Period. — Three four-day periods. The first exposure to superficial X rays was given on the third day of the third period.

X Ray Therapy.—One exposure to superficial X rays was given on the eleventh day of the experimental study,[1] and one exposure to deep X rays on the thirty-second day.[2]

[1] Dosage of superficial X rays was as for Darcia T.

[2] Dosage of deep X rays: Kilovolts, 210; milliampères, 15; filter, one millimetre of copper and one millimetre of aluminium; time, five minutes to left cervical field at 300 *r*. and five minutes to right cervical field at 300 *r*.

TABLE VIII.

Dulcie S., female, married, aged 17 years. Admitted to Metabolic Ward January 8, 1933. Discharged March 30, 1933. Diagnosis: Hyperthyreoidism.

Period Number.	Footnote Index.	Food Intake per Per'd. Cals.	Fluid Volume per Diem. C.cm.	Urine Volume per Per'd. C.cm.	Wgt. of Dried Fæces. Grms.	Basal Metabolic Rate. %	Basal Pulse Rate.	Wgt. Kilograms.	Calcium Metabolism per Period.						Phosphorus Metabolism per Period.						Nitrogen Metabolism per Period.						Blood Chemistry.	
									Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Calcium. Mgm. %	Inorganic Phosph'us Mgm. %
										Urine. Grms.	Stool. Grms.	Balance. Grms.				Urine. Grms.	Stool. Grms.	Balance. Grms.				Urine. Grms.	Stool. Grms.	Balance. Grms.				
0	1	5,050	1,600																									
1		10,730	1,600	4,190	66·6	+60·0	134	34·4	2·36	0·41	2·03	−0·08	17·4	86·0	3·86	3·41	0·93	−0·48	88·4	24·1	37·6	37·2	3·8	−3·4	98·9	10·1	11·4	6·3
2		10,730	1,600	6,340	79·0	+54·5	136	34·6	2·52	0·40	2·02	−0·10	15·9	80·2	3·92	3·22	0·91	−0·21	82·2	23·2	41·1	39·6	5·1	−3·6	96·3	12·4		
3		10,730	1,600	6,120	101·0	+61·5	128	34·3	2·13	0·32	2·14	−0·33	15·0	100·5	3·30	3·45	1·18	−1·33	104·6	35·7	34·1	41·0	5·4	−12·2	120·2	15·8		
4		10,730	1,600	6,480	101·0	+61·5	120	34·3	2·15	0·37	2·36	−0·58	17·2	109·7	3·74	3·63	1·11	−1·0	97·1	29·7	37·6	39·4	6·0	−7·6	104·8	16·0		
5		11,670	1,600	7,300	89·5	+50·0	120	33·7	2·37	0·43	2·32	−0·38	18·1	97·9	4·03	3·48	1·14	−0·59	86·4	28·3	40·9	38·5	6·9	−6·4	94·2	14·4		
6		11,607	1,600	9,000	116·5	+67·0	110	33·4	2·47	0·41	2·73	−0·67	16·6	110·5	4·01	3·35	1·33	−0·67	83·5	33·2	40·9	34·8	7·5	−1·4	85·1	18·3		
7		11,670	1,600	7,640	114·0	+62·0	114	33·4	2·22	0·56	2·26	−0·62	25·2	102·7	4·11	3·40	1·16	−0·45	82·7	28·2	40·9	36·4	6·6	−1·1	89·0	18·1		
8		11,670	1,600	6,680	105·0	+64·0	114	33·5	2·54	0·57	2·41	−0·44	32·5	94·9	4·14	3·43	1·13	−0·42	82·8	27·3	40·9	36·9	6·5	−3·2	90·2	15·9		
9		12,830	1,600	6,150	115·4	+56·0	120	33·5	2·41	0·53	2·49	−0·61	22·0	103·3	4·23	3·00	1·27	−0·04	70·9	30·0	45·0	32·6	7·2	+5·1	72·4	16·0		
10		12,830	1,600	6,770	100·5	+45·5	128	33·7	2·43	0·55	2·41	−0·53	22·6	99·2	4·43	3·13	1·07	+0·23	70·9	24·2	45·0	32·6	7·3	+5·1	72·4	16·2		
11		12,830	1,600	6,440	95·8	+44·0	128	33·2	2·57	0·61	2·63	−0·67	23·7	102·3	4·35	3·45	1·07	−0·17	79·3	24·3	45·0	36·8	7·5	+0·7	81·8	13·1		
12		12,830	1,600	5,650	112·4	+33·5	110	34·3	2·80	0·85	2·96	−0·98	28·9	102·7	4·27	3·45	1·39	−0·57	80·8	32·5	45·0	37·6	7·5	−0·1	83·6	13·6		
13		12,830	1,600	6,570	111·2	+29·0	136	34·5	2·94	0·69	3·02	−0·93	28·9	105·7	4·46	3·46	1·41	−0·41	77·6	31·6	45·0	35·3	7·4	+2·7	78·5	13·4		
14		12,830	1,600	8,260	103·0	+35·0	126	34·4	2·76	0·60	2·70	−0·63	25·0	97·8	4·37	2·95	1·31	−0·11	67·5	30·0	45·0	31·2	6·8	+7·0	69·3	15·1		
15		12,830	1,600	9,080	96·0	+35·0	104	35·0	2·43	0·60	2·65	−0·82	24·7	109·0	4·31	2·68	1·46	+0·15	62·2	34·3	45·0	28·5	6·8	+10·0	63·4	14·4		
16		12,830	1,600	9,420	103·0	+15·5	96	36·2	2·68	0·48	2·57	−0·37	17·9	95·5	4·18	2·45	1·37	+0·36	58·6	32·8	45·0	25·1	6·8	+13·1	55·8	15·1		
17		12,830	1,600	7,600	114·0	+9·5	104	36·8	2·56	0·42	2·84	−0·70	16·4	111·0	4·45	2·80	1·36	+0·19	65·2	30·5	45·0	25·3	7·4	+12·6	56·2	15·8		
18		12,830	1,600	6,860	126·0	−1·0	96	37·3	2·44	0·37	2·43	−0·36	15·2	99·6	4·21	2·69	1·18	+0·34	63·9	28·0	45·0	27·9	7·4	+9·7	62·0	16·4		
19		12,830	1,600	7,470	114·5	+18·0	104	38·2	2·62	0·37	2·67	−0·42	14·1	101·9	4·01	2·72	1·02	+0·27	67·8	25·5	45·0	28·0	6·9	+10·1	62·2	15·3		
						+23·0	112	38·3																				

a Exposure to superficial X ray on third day of period.
b Exposure to deep X ray on fourth day of period.
c Lugol's iodine, 1·8 cubic centimetres daily from first day to end of study.

1 On experimental diet for two days—specimens not saved.
2 One specimen of stool (approximately one-twelfth of whole period) lost.

N.B.—Periods were of four days' duration, in this and succeeding protocols, unless otherwise stated.

Wgt. = Weight. Kilograms. Phosph'us = Phosphorus. Per'd. = Period. Cals. = Calories. C.cm. = Cubic centimetres. Grms. = Grammes. Mgm. = Milligrammes.

Iodine Therapy.—Beginning on the fifty-seventh day of the experimental study and continuing for six four-day periods, when the study terminated, 1·8 cubic centimetres of Lugol's iodine were given daily. This patient was under observation for seventy-six consecutive days.

Metabolism During Fore-Period.—Basal metabolism was constant in the vicinity of +60%. The basal pulse rate remained in the vicinity of 130 per minute.

Weight was constant at 34·4 kilograms.

Nitrogen balance was slightly negative, −1·4 grammes *per diem* approximately.

Phosphorus balance was slightly negative, −0·17 gramme *per diem* approximately.

Calcium balance was very slightly negative, −0·04 gramme *per diem* approximately.

The results are not quite accurate, as one small stool, representing about one-twelfth of the total fæces for the second period, was lost. The error from this accident is, however, of no moment in dealing with the average balance over the twelve days; the error would be less than 1% for nitrogen and phosphorus and less than 3% for calcium.

Metabolism Following the Application of Superficial X Rays.—Basal metabolism showed fluctuations which were irregular, range +50% to +67%. The weather was at times very humid and probably influenced the result in several ways. On the whole the X rays had very little effect. The pulse rate tended to fall at first and then to rise.

Weight fell to 33·3 kilograms during the second period, but by increasing the diet the weight was then maintained.

Nitrogen balance was negative for the first two periods, but equilibrium was practically reached when the diet was increased.

Phosphorus balance was practically unaffected, the average daily loss for the five periods being 0·157 gramme. The loss during the last two periods was only 0·109 gramme *per diem*, this smaller excretion being probably influenced by the smaller negative nitrogen balance.

Calcium balance: The negative balance increased to an average of −0·135 gramme *per diem*. The rate of loss was practically constant throughout the five periods.

Metabolism Following the Application of Deep X Rays.—It was thought that the superficial X rays had succeeded in stimulating the parathyreoid apparatus without having any effect on the thyreoid gland; we decided to give a maximal dose of deep X rays in an attempt to depress the parathyreoid apparatus. This was quite unsuccessful, as we stimulated the parathyreoid and depressed the thyreoid gland. We were disappointed till we appreciated that the result obtained afforded further evidence in favour of our thesis, and in a manner which is very illustrative of the complex results induced by a therapeutic measure employed for a specific purpose.

Basal metabolism fell steadily from +56% immediately before the deep X rays were given to +29% during the fifth period. The pulse rate rose from 120 to 136 per minute. This increase in pulse rate is probably of definite significance. It is in keeping with the phenomenon of a falling pulse rate and gain of weight with a rising metabolism noticed by Hansman[39] in certain patients treated with X ray therapy.

Weight increased slowly to 34·5 kilograms by the fifth period, but at the beginning of this deep X ray period the diet was increased to 3,210 calories, and as the metabolism was falling she was receiving a diet in excess of the calculated requirements. The gain in weight was really much smaller than would have been expected.

Nitrogen balance became permanently positive immediately the diet was increased. The average gain during five periods was 0·755 gramme *per diem*.

Phosphorus balance approached equilibrium and was actually positive during the second period, but then became progressively negative. The average negative balance was 0·048 gramme *per diem*. The change in phosphorus balance was accounted for by the nitrogen balance becoming positive.

Calcium balance became increasingly more negative in spite of the falling metabolism, the gain in weight, the nitrogen balance becoming positive and the phosphorus balance approaching equilibrium. The average negative calcium balance was 0·185 gramme *per diem*; during the last two periods when the basal metabolic rate was lowest the loss of calcium was 0·234 gramme *per diem*.

Metabolism During the Administration of Lugol's Iodine.— Iodine was given because the physician in charge was not satisfied with her general condition. The iodine had a marked effect on her total metabolism but no effect on her calcium metabolism.

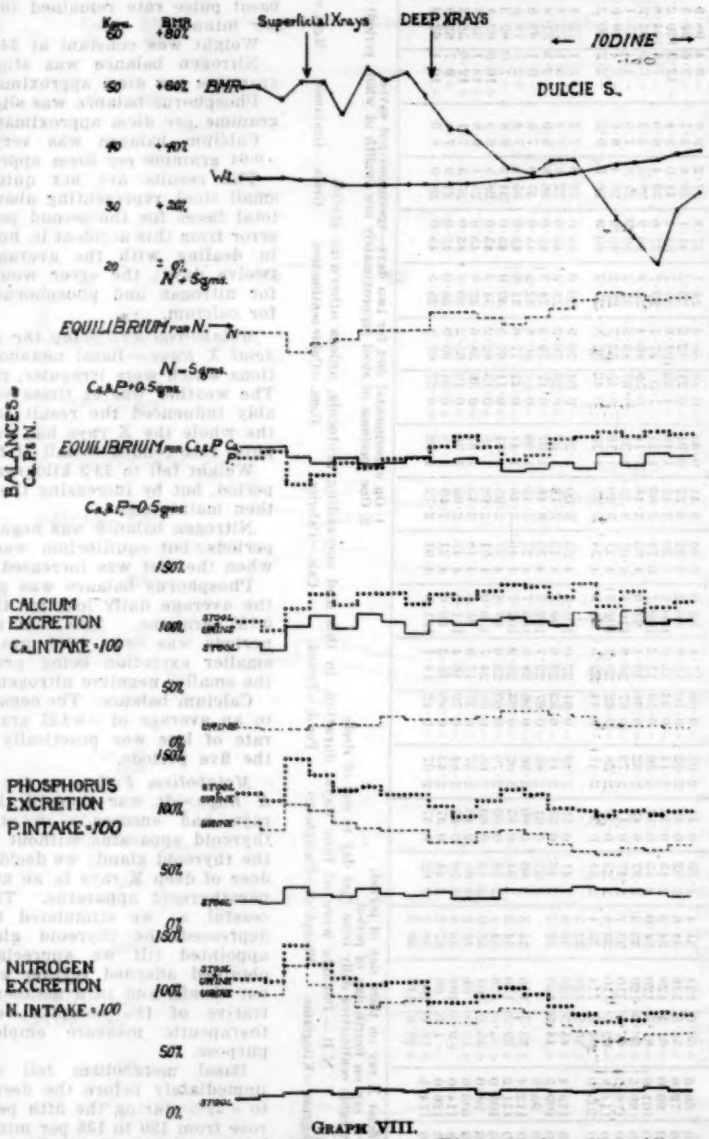
Basal metabolism, after a lag of four days, fell rapidly, and by the eighteenth day was −1%, but the good effect wore off immediately and three days later the basal metabolic rate was +18%, and in another four days +23%. The basal pulse was not affected to the same extent, the lowest observation being as high as 96 beats per minute.

Weight increased rapidly and in the twenty-five days she gained 3·9 kilograms. However, in the last four days she gained only 0·1 kilogram.

Nitrogen balance became markedly positive and for the six four-day periods the average gain was 2·6 grammes *per diem*. During the last two periods when the metabolism was rising, nitrogen storage continued at the same rate, the average gain being 2·0 grammes *per diem*.

Phosphorus balance became immediately positive and the average gain for the six periods was 0·06 gramme *per diem*. The storage of phosphorus had no direct relationship to the falling metabolism, and was probably controlled by the amount of nitrogen stored.

Calcium balance remained negative; the average loss *per diem* for the six periods was 0·138 gramme. The rate of loss was therefore comparable to that obtaining at the time when the first exposure to X rays was having effect and when the basal metabolic rate was in the vicinity of +60%. Furthermore, as will be appreciated by an inspection of the protocols, the calcium loss was independent of the varying effect the iodine was having on the total metabolism.



GRAPH VIII.

Dulcie S., female, married, aged seventeen. Diagnosis: hyperthyreoidism.

This patient's mineral metabolism was remarkable in many respects. There was only a small negative calcium balance during the whole experimental period, and though the basal metabolism ranged from +67% to −1%, the amount of calcium loss was not appreciably affected. The application of both superficial and deep X rays was followed by an increased loss of calcium, though the basal metabolic rate was falling.

There can be no doubt that there must have been a definite calcium lack, as this patient, while still quite adolescent, had had a chronic drainage on her calcium stores since the age of fifteen, firstly by her pregnancy, secondly by a long period (twenty months) of lactation, thirdly by the association of a negative calcium balance with hyperthyreoidism. In spite of the drainage there was no evidence of osteoporosis elicited by radiographic examination of her bones. This, however, does not mean that there was no deficiency in calcification, as the drainage of calcium has to be very severe over many years before radiographic evidence of osteoporosis is definite.

TABLE IX.

Jean McL., female, single, aged 22 years. Admitted to Metabolic Ward November 10, 1932. Discharged December 23, 1932. Diagnosis: Hyperthyreoidism.

Period Number.	Footnote Index.	Food Intake per Per'd. Cals.	Fluid Intake per Diem. C.cm.	Urine Volume per Per'd. C.cm.	Wgt. of Dried Feces. Grms.	Basal Metabolic Rate. %	Basal Pulse Rate.	Wgt. Kilograms.	Calcium Metabolism per Period.					Phosphorus Metabolism per Period.					Nitrogen Metabolism per Period.					Blood Chemistry.	
									Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Balance. Grms.	Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Balance. Grms.	Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion. Urine. Grms.	Excretion. Stool. Grms.	Balance. Grms.	Ratio Urine to Intake. %	Ratio Stool to Intake. %	Calcium. Mgm. %	Inorganic Phosph'us. Mgm. %
0	1	8,750	1,500	4,020	109·5	+57·0	108	51·5	2·24	0·98	2·44	−1·18	43·7	108·9	3·67	3·05	1·22	−0·60	83·1	33·2	37·6	6·5	1·0	80·1	17·3		
1–2	4	10,730	1,500	6,100	87·5	+46·0	96	50·6	2·28	1·99	2·12	−1·83	87·3	92·9	4·10	4·72	1·07	−1·69	115·1	26·1	40·9	5·1	−13·7	121·1	12·5		
2–3		11,670	1,500	5,550	110·5	+34·0	100	50·6	2·24	1·73	2·70	−1·66	62·4	97·5	4·10	4·11	1·36	−1·37	100·2	33·2	40·9	6·8	−5·7	96·6	16·6		
3–4		11,670	1,500	5,560	149·5	+38·0	88	50·7	2·77	2·35	3·67	−3·25	84·8	132·5	4·40	4·25	1·88	−1·66	95·1	42·1	45·0	8·9	−4·9	91·1	19·8		
4–5	2	12,880	1,500	6,250	121·5	+41·0	104	50·9	3·40	2·34	3·98	−2·92	68·8	117·0	5·35	5·14	1·91	−1·70	96·1	35·7	57·0	9·3	−1·3	85·9	16·3		
5–6	2	16,040	1,500	7,810	151·0			52·1	3·79	2·14	3·00	−1·77	54·7	107·5	4·37	4·26	1·45	−1·39	97·9	33·9	45·0	7·7	−4·66	91·8	17·1		
6–7	c	12,880	1,500	5,300	129·3	+31·0	94		3·00	1·64	3·13	−1·77	54·7	104·3	4·06	3·82	1·49	−1·25	94·1	30·7	45·0	7·5	−2·5	89·3	16·7		
7–8	d	12,880	1,500	5,880	104·8	+30·0	104		3·60	1·42	2·68	−1·50	54·6	103·1	4·27	3·81	1·30	−0·84	89·2	30·5	45·0	6·5	+1·6	82·1	14·4		
8–	e	12,880	1,500	5,990		+30·0	104	51·7	2·45	1·42			58·0		4·21	4·13			96·1		45·0			74·9			
	3, 5																										

a Exposure to deep X ray on third and fourth day of period.
b Exposure to deep X ray on second and fifth day of period.
c Exposure to deep X ray on second and fourth day of period.
d Exposure to deep X ray on third day of period.
e Exposure to deep X ray on first day of period.

1 On experimental diet for three days—specimens not saved.
2 Five-day period.
3 Stool for this period spoilt.
4 Menses began on third day of period and continued for five days.
5 Menses began on third day of period.

N.B.—Periods were of four days' duration, in this and succeeding protocols, unless otherwise stated.

Wgt. = Weight. Kilogrms. = Kilograms. Phosph'us = Phosphorus. Per'd. = Period. Cals. = Calories. C.cm. = Cubic centimetres. Grms. = Grammes. Mgm. = Milligrammes.

Calcium elimination was predominantly fæcal, but when the calcium loss increased the percentage change in urinary excretion was greater than that in fæcal excretion.

GRAPH IX.

Jean McL., female, single, aged twenty-two. Diagnosis: hyperthyreoidism.

The phosphorus balance bore a direct relationship to the nitrogen balance, falling and rising *pari passu* with the negative or positive nitrogen balance.

While the findings in this patient afford definite evidence that hyperthyreoidism does not have any specific effect on calcium metabolism, they illustrate further that hyperthyreoidism may not always be associated with hyperparathyreoidism, and that changes in the production of thyroxin may not always be associated with changes in the parathyreoid apparatus. During the fore-period this patient was practically in calcium equilibrium in spite of a severe hyperthyreoidism. It is more than probable that if a wide series of hyperthyreoidic patients were studied, some would be found with a positive calcium balance, just as hyperthyreoidism may be associated with hyperactivity or hypoactivity of other endocrine glands.

CASE IV.—Jean McL. was a female aged twenty-three. (For history see case report.) The estimated caloric requirement (basal × 3/2) = 3,150. The caloric intake was 2,700 for the first period, 2,910 for the second and third periods, 3,210 for the remaining periods. The diet was increased without the patient's knowledge on account of slight loss of weight and a negative nitrogen balance. The fluid intake was 1,500 cubic centimetres daily. (For experimental details see Table IX and Graph IX.)

Fore-Period.—Three four-day periods. Rest in bed, no medication.

X Ray Therapy.—Five four-day periods, one five-day period (second period). Eight exposures to deep X rays were given.[1] (For dates see protocols.)

Metabolism During Fore-Period.—Basal metabolism fell steadily from +57% to +34%. The basal pulse remained fairly constant, in the vicinity of 100 per minute.

Weight: There was a slight loss during the first period, but thereafter the weight was constant.

Nitrogen balance varied considerably; average −1·5 grammes *per diem*; range +0·25 to −3·9 grammes *per diem*.

Phosphorus balance was definitely negative for each period; average −0·305 gramme *per diem*; range −0·15 to −0·42 gramme *per diem*.

Calcium balance was definitely negative for each period; average −0·390 gramme *per diem*; range −0·30 to −0·46 gramme *per diem*.

Metabolism During X Ray Therapy.—Basal metabolism remained remarkably constant, in the vicinity of +35%,

[1] X ray dosage: Kilovolts, 210; milliampères, 15; filter, one centimetre copper and one centimetre of aluminium; 800 *r.* to right thyreoid field, 800 *r.* to the left thyreoid field in all.

TABLE X.

Edith A., female, married, aged 36 years. Admitted to Metabolic Ward July 7, 1932. Discharged October 18, 1932. Diagnosis: Chronic Hyperthyreoidism associated with Hypoparathyreoidism.

Period Number	Footnote Index.	Food Intake per Per'd. Cals.	Fluid Volume per Day. C.cm.	Urine Volume per Per'd. C.cm.	Wgt. of Dried Feces. Grms.	Basal Metabolic Rate. %	Basal Pulse Rate.	Wgt. Kilograms.	Calcium Metabolism per Period.						Phosphorus Metabolism per Period.						Nitrogen Metabolism per Period.						Blood Chemistry.	
									Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Calcium. Mgm. %	Inorganic Phosphorus. Mgm. %
										Urine. Grms.	Stool. Grms.	Balance. Grms.				Urine. Grms.	Stool. Grms.	Balance. Grms.				Urine. Grms.	Stool. Grms.	Balance. Grms.				
0–1		14,000	1,300	6,100	127·6	+64·0	112	53·7	2·47	0·56	2·08	−0·17	22·6	84·2	4·53	2·95	1·25	+0·33	65·3	27·6	47·7	37·8	6·0	+3·9	79·3	12·6		
1–2		14,000	1,300	6,525	96·5	+60·0	108	53·5	2·50	0·54	2·22	−0·24	21·6	88·0	4·91	3·21	1·34	+0·46	65·4	29·7	48·7	38·9	6·7	+3·1	80·0	13·8		
2–3		14,000	1,300	7,600	86·0	+64·0	120	54·8	2·55	0·45	2·12	−0·02	17·6	83·1	4·80	3·23	1·29	+0·28	67·3	26·9	48·8	36·2	6·5	+6·1	74·2	13·3		
3–4		17,500	1,300	8,965	114·3	+64·0	128	54·6	3·35	0·53	2·61	+0·21	15·8	77·9	5·91	4·48	1·58	−0·15	75·8	26·7	62·3	47·7	8·0	+6·6	76·6	12·8		
4–5		11,400	1,300	6,660	122·7	+64·0	124	54·4	2·64	0·37	2·64	−0·37	14·0	100·0	3·97	3·40	1·66	−0·68	77·6	35·0	43·1	43·1	7·7	+5·6	77·1	13·8		
5–6		16,170	1,300	4,300	86·0	+59·0	116	54·6	2·04	0·16	2·07	−0·19	8·0	105·0	5·13	3·21	1·42	+0·59	55·7	39·5	45·4	26·3	5·6	+13·5	57·7	13·5		
6–7	4a	16,170	1,300	6,520	104·4	+58·0	136	55·0	2·84	0·41	2·45	−0·02	14·5	86·3	5·13	3·23	1·42	+0·48	63·0	27·7	54·5	40·2	7·4	+7·0	74·2	11·5	9·7	5·8
7–8	4b	16,170	1,300	7,410	93·0	+60·0	124	55·8	2·96	0·41	2·02	+0·53	14·0	68·4	5·09	3·23	1·14	+0·72	63·5	22·4	51·9	38·0	6·6	+7·6	73·8	12·7	10·5	5·5
8–9	4c	16,170	1,300	7,160	105·0	+63·0	104	55·8	2·92	0·36	2·29	+0·27	12·3	78·4	5·12	3·28	1·23	+0·61	64·1	24·0	52·7	41·3	6·6	+4·0	78·9	13·5		
9–10	5	16,170	1,300	7,040	105·4	+60·0	112	55·8	2·90	0·33	2·21	+0·36	11·4	76·2	5·19	3·28	1·22	+0·69	63·2	23·5	53·2	37·3	7·1	+8·0	70·2	13·5	10·0	4·75
10–11	6	16,170	1,300	7,480	109·0	+49·0	116	56·7	2·74	0·33	1·97	+0·44	12·0	71·9	5·00	3·51	1·11	+0·38	70·2	22·2	53·3	39·3	6·9	+6·9	71·9	13·2		
11–12	7	16,170	1,300	7,720	114·0	+41·0	108	57·3	2·69	0·26	2·21	+0·22	9·7	82·2	4·96	3·45	1·18	+0·33	69·5	23·8	53·3	39·8	7·5	+6·0	74·8	13·7	10·3	4·64
12–13	8	16,170	1,300	7,250	134·5	+41·0	108	56·6	2·70	0·28	2·23	+0·19	10·4	82·6	4·96	3·55	1·28	+0·13	71·6	25·8	53·3	42·8	7·8	+3·2	80·4	14·7		
13–14	9	16,170	1,300	7,700	98·1	+28·0	108	57·2	2·87	0·34	2·01	+0·52	11·9	70·0	5·03	3·64	1·15	+0·24	72·4	22·9	53·3	43·3	7·5	+2·0	81·4	15·0		
14–15	10a	16,170	1,300	7,110	108·0	+32·0	100	57·3	2·73	0·25	2·26	+0·22	9·2	82·8	4·88	3·23	1·22	+0·43	66·2	25·0	53·3	38·2	6·1	+8·0	71·8	18·0	9·9	4·8
15–16	10b	14,000	1,200	7,270	91·7	+31·0	100	57·3	2·86	0·31	2·26	+0·49	10·8	79·0	4·96	3·14	1·05	+0·77	63·3	21·2	49·1	36·6	6·4	+6·4	74·5	12·4	10·7	4·84
16–17	11c	14,000	1,200	7,120	95·7	+38·0	88	58·1	2·87	0·28	2·02	+0·57	9·8	70·4	4·82	3·14	1·06	+0·62	65·1	22·2	49·1	37·5	6·3	+5·3	70·4	13·8	10·4	4·08
17–18		14,000	1,200	6,400	107·8	+28·0	92	58·8	2·89	0·28	1·33	+1·02	10·6	50·6	4·60	3·34	0·72	+0·54	72·6	15·7	49·1	36·7	4·6	+7·8	74·7	9·4		
18–19	12a	14,000	1,200	7,300	100·3	+31·0	88	58·8	2·91	0·29	2·17	+0·45	10·0	74·5	4·45	3·68	1·07	−0·30	82·7	24·0	49·1	40·5	6·5	+2·1	82·5	13·2		
19–20	13	14,000	1,300	7,100	109·10	+39·0	88	58·5	3·26	0·29	2·32	+0·65	8·9	71·2	4·70	3·66	1·10	−0·06	77·9	23·4	49·1	41·5	7·0	+0·6	84·5	14·3	9·8	4·89
20–21	14																										10·1	4·11

a Irradiated ergosterol, 3 milligrammes daily, beginning first day of eighth period, and continuing till last day of fifteenth period.
b Irradiated ergosterol, 6 milligrammes daily, beginning first day of sixteenth period and continuing till last day of seventeenth period.
c Irradiated ergosterol, 9 milligrammes daily, beginning first day of eighteenth period and continuing till last day of nineteenth period.
d Irradiated ergosterol suspended.
1 On experimental diet for four days—specimens not saved.
2 A five-day period.
3 A three-day period.
4 Blood taken before the administration of irradiated ergosterol commenced.
8, 9, 13, 14 Blood taken on first day of period.
6, 11 Blood taken on third day of period.
5, 10 Blood taken on fourth day of period.
7 Menses began on first day of period and continued for five days.
12 Menses began on first day of period and continued for four days.

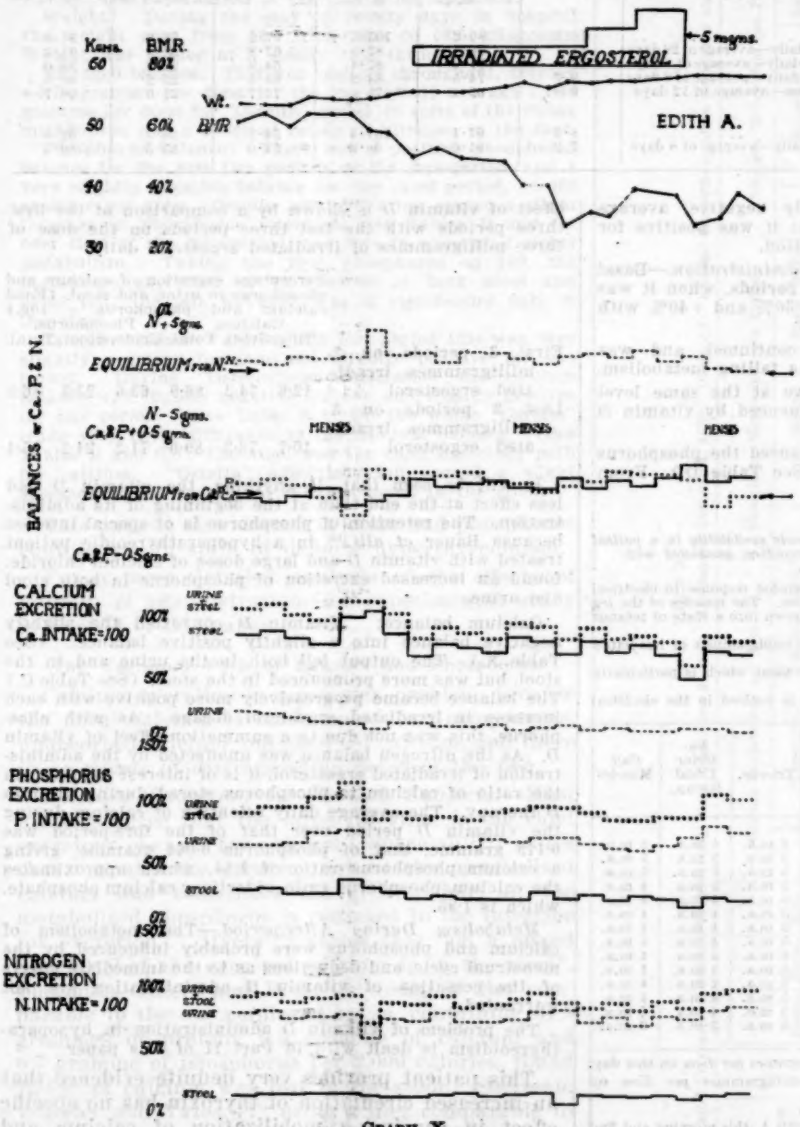
N.B.—Periods were of four days' duration, in this and succeeding protocols, unless otherwise stated.

Wgt. = Weight. Kilogrms. = Kilograms. Phosph'us = Phosphorus. Per'd = Period. Cals. = Calories. C.cm. = Cubic centimetres. Grms. = Grammes. Mgm. = Milligrammes.

the range being +31% to +41% over a period of twenty-four days. The pulse rate also remained constant in the vicinity of 100 beats per minute.

Weight increased very slowly but steadily from 50·6 kilograms to 52·3 kilograms. There was a slight fall in the period after the X ray exposures ceased.

Nitrogen balance was practically in equilibrium; the average loss was −0·53 gramme *per diem;* range +0·4 to −1·2 grammes *per diem.*



GRAPH X.

Edith A., female, married, aged thirty-six. Diagnosis: chronic hyperthyreoidism associated with hypoparathyreoidism.

Phosphorus balance: The negative balance was slightly increased over that of the fore-period, the average daily loss being 0·326 gramme *per diem;* range −0·42 to −0·21 gramme *per diem.* There was no change in the ratio of fæcal to urinary output.

Calcium balance: The negative balance was very definitely increased over that of the fore-period, the average daily loss being 0·561 gramme *per diem;* range −0·81 to −0·38 gramme. As with the phosphorus balance, there was a tendency for the loss to become less as the therapy continued. The increased loss was caused by an augmented output in both urine and stool.

The results from this patient provide further evidence of the independence of calcium and phosphorus metabolism and thyreoid function. During X ray therapy, though the basal metabolic rate was on the whole lower than during the fore-period, the negative calcium balance was greater. We interpret the results as indicating that the X rays had stimulated the parathyreoid glands and had had a negligible effect on the thyreoid gland. The subsequent history of the patient shows that the X rays had no delayed effect on the thyreoid gland, as when she was readmitted sixty-two days later, having rested at home in the *interim,* the basal metabolic rate was still +36%, and the clinical condition was unchanged.

Hyperthyreoidism Associated with Hypoparathyreoidism.—There were two cases of hyperthyreoidism associated with hypoparathyreoidism.

CASE I.—Edith A. was a female, married, aged thirty-six. (For history see case report.) The estimated caloric requirement (basal × ⅔) = 3,400. The caloric intake was 3,500 for four periods, 3,800 for the next eleven periods, 3,500 for the last six periods. The fluid intake was 1,200 cubic centimetres daily. (For experimental details see Table X and Graph X.)

Fore-Period.—Seven periods, five of four days, one of five and one of three days. Rest in bed, no medication.

Vitamin D Therapy.—Seven four-day periods on three cubic centimetres of "Radiostol" daily,[1] two four-day periods on six cubic centimetres of "Radiostol" daily, and two four-day periods on nine cubic centimetres of "Radiostol" daily.

After-Period. — Three four-day periods, rest in bed, no medication. This patient was under observation for eighty-four consecutive days.

Metabolism During Fore-Period.—Basal metabolism was constant in the vicinity of +64% during the first four periods, and then fell steadily during the remaining three periods to +50%.

Weight steadily increased.

Nitrogen balance was positive to the extent of one gramme *per diem,* and was unaffected by the fall of the metabolism.

Phosphorus balance was positive, except in the period that followed menstruation.

[1] "Radiostol": One cubic centimetre = one milligramme irradiated ergosterol = 10,000 antirhachitic units (international).

TABLE C.

Showing the effect of the administration of vitamin D on the excretion of calcium and phosphorus in urine and stool (expressed as a percentage of the intake) in patients suffering from chronic hyperthyreoidism associated with hypoparathyreoidism.

	Calcium.			Phosphorus.		
	Urine Percentage.	Stool Percentage.	Total Percentage.	Urine Percentage.	Stool Percentage.	Total Percentage.
Edith A.						
Fore-period—average of 28 days	16·3	89·2	105·5	67·2	28·8	96·0
"Radiostol" administration, 3 cubic centimetres daily—average of 28 days	11·7	76·1	87·8	67·8	23·5	91·3
"Radiostol" administration, 6 cubic centimetres daily—average of 8 days	10·0	77·4	87·4	64·8	23·2	88·0
"Radiostol" administration, 9 cubic centimetres daily—average of 8 days	9·7	74·5	84·2	63·3	23·2	86·5
Following cessation of "Radiostol" administration—average of 12 days	9·8	65·4	75·2	77·7	21·0	98·7
Emma B.						
Fore-period—average of 12 days	8·3	97·1	107·4	54·1	38·7	92·8
"Ostelin" administration of 4 cubic centimetres daily—average of 8 days	7·2	91·0	98·2	54·0	35·5	89·5

Calcium balance was very slightly negative, average −0·028 gramme *per diem*, except that it was positive for the period coincident with menstruation.

Metabolism During Vitamin D Administration.—Basal metabolism continued to fall for six periods, when it was +28%. It then fluctuated between +30% and +40% with an upward trend.

Weight: The gain in weight continued, and was uninfluenced by the vitamin *D* or the falling metabolism.

Nitrogen balance continued positive at the same level as in the fore-period, and was uninfluenced by vitamin *D* administration.

Phosphorus balance: Vitamin *D* caused the phosphorus balance to become more positive. (See Table D.) From

TABLE D.

Showing the effect of irradiated ergosterol on muscle excitability in a patient (Edith A.) suffering from chronic hyperthyreoidism associated with hypoparathyreoidism.

August 8, 1932.—"The muscles give an exaggerated response to electrical stimulation characteristic of a tetany reaction. The muscles of the leg are particularly affected and are quickly thrown into a state of tetanus by the alternating current."
August 23, 1932.—The administration of three milligrammes of irradiated ergosterol daily commenced.
August 27, 1932.—"There is a marked improvement which is particularly noticeable in the leg muscles."
September 3, 1932.—"A further improvement is noticed in the electrical reactions."

Date.	Flexors of Wrists.	Extensors of Wrists.	Biceps.	Triceps.	Anterior Tibial Group.	Calf Muscles.
September 13	4 m.a.	5 m.a.	3 m.a.	4 m.a.	4 m.a.	3 m.a.
September 20(*a*)	4 m.a.	5 m.a.	4 m.a.	5 m.a.	5 m.a.	5 m.a.
September 27	4 m.a.	5 m.a.	4 m.a.	5 m.a.	5 m.a.	5 m.a.
September 30(*b*)	4 m.a.	4 m.a.	4 m.a.	5 m.a.	5 m.a.	4 m.a.
October 4	4 m.a.	4 m.a.	4 m.a.	5 m.a.	4 m.a.	4 m.a.
October 5	4 m.a.	4 m.a.	4 m.a.	5 m.a.	4 m.a.	4 m.a.
October 6(*c*)	4 m.a.	4 m.a.	4 m.a.	5 m.a.	4 m.a.	4 m.a.
October 7	4 m.a.	4 m.a.	4 m.a.	5 m.a.	4 m.a.	4 m.a.
October 10	4 m.a.	4 m.a.	4 m.a.	5 m.a.	4 m.a.	4 m.a.
October 12	4 m.a.	4 m.a.	4 m.a.	5 m.a.	4 m.a.	4 m.a.
October 16	4 m.a.	4 m.a.	4 m.a.	5 m.a.	4 m.a.	4 m.a.
October 18	4 m.a.	4 m.a.	4 m.a.	5 m.a.	4 m.a.	4 m.a.
October 25	4 m.a.	4 m.a.	4 m.a.	5 m.a.	4 m.a.	4 m.a.
November 1(*d*)	3 m.a.	4 m.a.	3 m.a.	3 m.a.	3 m.a.	3 m.a.

(*a*) Irradiated ergosterol increased to six milligrammes *per diem* on this day.
(*b*) Irradiated ergosterol increased to nine milligrammes *per diem* on September 28.
(*c*) Irradiated ergosterol suspended on this day.
(*d*) The masseuse reported: "I have tested Edith A. this morning and find that she is now taking a milliampère less than when she was receiving irradiated ergosterol. The increase in excitability of the muscles has been gradual."

m.a.—milliampères.

a study of the excretion of phosphorus in stool and urine expressed as a percentage of the intake (Table C) it will be seen that the change in phosphorus balance was effected by a decreased urinary and fæcal output, the change in the fæces being somewhat more marked. Each increase in dose of vitamin *D* caused a further storage of phosphorus. That this was not simply a summation effect of vitamin *D* is shown by a comparison of the first three periods with the last three periods on the dose of three milligrammes of irradiated ergosterol daily.

	Percentage excretion of calcium and phosphorus in urine and stool. (Food calcium and phosphorus = 100.)					
	Calcium.			Phosphorus.		
	Urine.	Stool.	Total.	Urine.	Stool.	Total.
First 3 periods on 3 milligrammes irradiated ergosterol	12·6	74·3	86·9	63·6	23·3	86·9
Last 3 periods on 3 milligrammes irradiated ergosterol	10·7	78·3	89·0	71·2	24·2	95·4

It will be seen that, if anything, the vitamin *D* had less effect at the end than at the beginning of its administration. The retention of phosphorus is of special interest because Bauer *et alii*,[13] in a hypoparathyreoidic patient treated with vitamin *D* and large doses of calcium chloride, found an increased excretion of phosphorus in both stool and urine.

Calcium balance: Vitamin *D* converted the slightly negative balance into a slightly positive balance. (See Table X.) The output fell both in the urine and in the stool, but was more pronounced in the stool. (See Table C.) The balance became progressively more positive with each increase in irradiated ergosterol dosage. As with phosphorus, this was not due to a summation effect of vitamin *D*. As the nitrogen balance was unaffected by the administration of irradiated ergosterol, it is of interest to ascertain the ratio of calcium to phosphorus stored during vitamin *D* therapy. The average daily retention of calcium during the vitamin *D* period over that of the fore-period was 0·119 gramme, that of phosphorus 0·064 gramme, giving a calcium/phosphorus ratio of 1·84, which approximates the calcium/phosphorus ratio of tertiary calcium phosphate, which is 1·93.

Metabolism During After-period.—The metabolism of calcium and phosphorus were probably influenced by the menstrual cycle, and deductions as to the immediate effects of the cessation of vitamin *D* administration are not warranted.

The problem of vitamin *D* administration in hypoparathyreoidism is dealt with in Part II of this paper.

This patient provides very definite evidence that an increased circulation of thyroxin has no specific effect in causing a mobilization of calcium and phosphorus from the bones. In spite of a severe hyperthyreoidism, as manifested by the presence of all the classical signs and symptoms of the disease and a constantly elevated metabolism, this patient over a period of eighty-four consecutive days was in calcium and phosphorus equilibrium.

CASE II.—Emma B. was a female, married, aged fifty-one. (For history see case report, and previous case report.[10]) The estimated caloric requirement (basal × 3/2) = 2,330.

The caloric intake was 2,640 *per diem*. The fluid intake was 1,150 cubic centimetres *per diem*. (For experimental details see Table XI and Graph XI.)

Fore-period.—Three four-day periods.

Vitamin D Therapy.—Two four-day periods on four cubic centimetres ostelin daily[1]

Basal metabolism: This remained practically constant at +25% for the first three periods and then rose during vitamin *D* administration to +34%, and fell again to +27%. The explanation of the rise is not apparent.

Weight: During the stay of twenty days in hospital the weight rose from 52·4 kilograms to 53·5 kilograms. Weight was gained at a steady rate throughout.

Nitrogen balance: This was positive throughout, average +0·74 gramme *per diem* for the fore-period; average +1·46 gramme *per diem* for "Ostelin"-period, in spite of the rising metabolism, and a constant intake of nitrogen in the food.

Phosphorus balance: There was a positive phosphorus balance for the first two periods of the fore-period, and a very slightly negative balance for the third period, —0·008 gramme *per diem*. Ostelin administration caused a slight increase in phosphorus retention (see Tables D and C) over that of the fore-period, and this in spite of a rising metabolism. Taking the food phosphorus as 100, the percentage excretion of phosphorus in both stool and urine fell; the fall, however, was of significance only in the stool.

Calcium balance: During the fore-period this was very slightly negative for two and slightly positive for one period. During "Ostelin" administration the calcium balance was slightly negative for one and slightly positive for one period. (See Table X.) On the whole "Ostelin" made very little difference to the calcium balance. (See Tables B and C.) The stool was the chief excretory path for calcium. "Ostelin" administration caused a slight decrease in the amount of calcium found in the stool.

This patient also showed calcium and phosphorus equilibrium in spite of definite hyperthyreoidism.

For a more detailed analysis of the effects of vitamin *D* administration, see experimental study in Part II of this paper.

The Excretory Path of Calcium and Phosphorus.

Calcium excretion is a complex problem, because the fæcal calcium is made up of two components, unabsorbed calcium and excreted calcium, and there is no means of distinguishing between the two.

Calcium Excretion in Normal Subjects.—Most workers agree that the large intestine is the chief excretory channel for calcium. Sherman[101] states that "usually the greater part of the metabolised calcium and sometimes the greater part of the metabolised phosphorus is returned to the intestine for excretion". Myers[46] states that "on a mixed diet 60% of the excreted calcium is in the stool". Sherman, Gillett and Pope,[105] using a diet comparable to the one employed by us, containing 61·9 grammes of protein, 0·3 gramme of calcium and 0·7 gramme of phosphorus per 2,000 calories, found 73·6% of calcium was lost in the stool. Sherman, Wheeler and Yates,[106] using a diet comparable to ours but somewhat low in calcium (0·14 gramme per day in Case I, 0·24 gramme per day in Case II), found 52% in the stool in one case, 57% in the other. Bassett, Elden and McCann[14] give results on two subjects, but these were for a five-day period without a fore-period. In our experience, such a short

[1] "Ostelin" = 5,000 antirhachitic units (international) per cubic centimetre. The "Ostelin" used in this research was kindly donated by Joseph Nathan & Co. (Aust.) Pty. Ltd., the proprietors of "Glaxo".

TABLE XI.

Emma B., female, married, aged 51 years. Admitted to Metabolic Ward September 9, 1932. Discharged October 4, 1932. Diagnosis: Chronic Hyperthyreoidism associated with Hypoparathyreoidism.

Period Number.	Footnote Index.	Food Intake per Per'd. Cals.	Fluid Intake per Diem. C.cm.	Urine Volume per Per'd. C.cm.	Wgt. of Dried Fæces. Grms.	Basal Metabolic Rate. %	Basal Pulse Rate.	Wgt. Kilogrms.	Calcium Metabolism per Period.						Phosphorus Metabolism per Period.						Nitrogen Metabolism per Period.						Blood Chemistry.	
									Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Intake. Grms.	Excretion.			Ratio Urine to Intake. %	Ratio Stool to Intake. %	Calcium. Mgm. %	Inorganic Phosphorus. Mgm. %
										Urine. Grms.	Stool. Grms.	Balance. Grms.				Urine. Grms.	Stool. Grms.	Balance. Grms.				Urine. Grms.	Stool. Grms.	Balance. Grms.				
0		7,840	1,150	4,860	89·5	+25·0	110	52·7	1·94	0·18	1·93	−0·17	9·3	99·5	3·5	1·92	1·36	+0·22	54·9	38·9	33·0	29·8	5·7	+2·5	78·4	15·0	10·8	4·33
1		10,450	1,150	4,860	71·5	+27·0	96	52·9	2·05	0·16	1·67	+0·22	7·8	81·5	3·56	2·08	1·17	+0·30	58·6	32·9	38·0	29·5	4·8	+3·7	77·6	12·6		
2		10,450	1,150	4,490	85·5	+25·0	104	53·3	2·15	0·15	1·67	−0·35	7·7	110·4	3·44	1·95	1·52	−0·03	56·9	44·3	38·0	29·4	5·9	+2·7	77·4	15·5	10·2	4·64
3	2	10,450	1,150	5,400	84·3	+33·0	100	53·5	2·21	0·14	2·17	−0·10	6·3	98·2	3·77	1·92	1·39	+0·46	50·9	36·9	38·0	26·6	5·5	+5·9	70·0	14·5	10·7	4·45
4	2	10,450	1,150	4,940	73·3	+27·0	100	54·2	2·23	0·18	1·87	+0·18	8·1	83·8	3·46	1·95	1·18	+0·30	57·2	34·1	38·0	27·4	4·8	+5·8	72·1	12·6	10·4	3·80

a Irradiated ergosterol, 4 milligrammes daily, beginning on first day of fourth period and continuing for two periods.

1 On experimental diet for three days—specimens not saved.

2 Blood taken on second day of period.

3 Blood taken on first day of period.

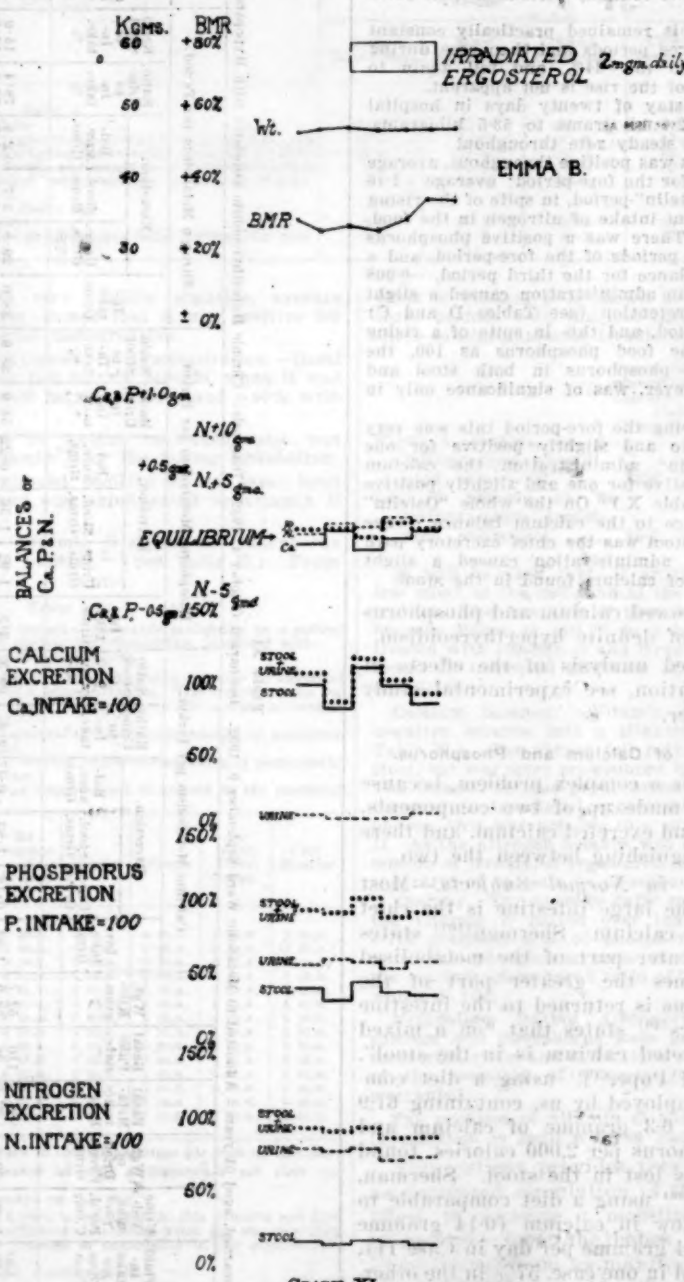
4 Blood taken on fourth day of period.

5 Blood taken three days after last day of period.

N.B.—Periods were of four days' duration, in this and succeeding protocols, unless otherwise stated.

Wgt. = Weight. Kilogrms. = Kilograms. Phosph'us = Phosphorus. Per'd = Period. Cals. = Calories. C.cm. = Cubic centimetres. Grms. = Grammes. Mgm. = Milligrammes.

period does not give an adequate idea of calcium and phosphorus balance. Their figures were: Case Z, 83·4%; Case S, 78·1%. Myers[46] investigated a series of fourteen people and found an average of 90%, and the range 80% to 94% of calcium in the fæces. Bogert and McKittrick[25] found variations according to the reaction of the ash of the food; in four normal persons, on a neutral diet which was very similar to the one employed by us, there was an average output of 70% of calcium in the fæces—range 55% to 78%. Bogert and Kirkpatrick,[24] in four persons different from those of the previous workers but on a similar diet, found an average of 74% calcium in the fæces—range 63% to 79%. Rose,[93] in four patients on a diet comparable to that of the above workers, found an average of 68%—range 56% to 78%. In the experiments of Aub and his coworkers,[15] in thirteen normal controls on a diet low in calcium and phosphorus, there was an average of 76% of calcium in the fæces—range 46·6% to 95·6%. In our two normal controls the average output of calcium in the stool was 67%—range 60% to 74%. Several workers have investigated the calcium excretion in infants.[109] [33] [117] [118] [119] [120] All found that the calcium output is predominantly fæcal.



GRAPH XI.

Emma B., female, married, aged fifty-one. Diagnosis: chronic hyperthyreoidism associated with hypoparathyreoidism.

Though calcium elimination is chiefly a function of the intestinal tract, the wide variations found in the ratio of fæcal calcium to urinary calcium would indicate that many factors govern this ratio. It seems probable that individual constitution is of great importance.

Calcium Excretion in Hyperthyreoidism.—When we come to hyperthyreoidic patients we find similar variations in the path of calcium elimination. Taking patients who have had no special treatment, in the material of Aub and his coworkers there are only two cases for consideration, as the other patients were given iodine almost immediately the experimental study began.

H.E.,[(a)] a male, had an average of 56% of calcium excreted in the fæces.

E.F.,[(c)] a female, had an average of 32·3% of calcium excreted in the fæces.

In seven patients of the present study, before medication:

D.S., a female, had an average of 85% of calcium excreted in the fæces.

D.E., a female, had an average of 70% of calcium excreted in the fæces.

J.McL., a female, had an average of 60% of calcium excreted in the fæces.

A.I., a male, had an average of 58% of calcium excreted in the fæces.

D.T., a female, had an average of 56·4% of calcium excreted in the fæces.

P.W., a female, had an average of 55% of calcium excreted in the fæces.

M.R., a female, had an average of 52% of calcium excreted in the fæces.

The highest percentages of fæcal calcium were found in our cases of hyperthyreoidism associated with hypoparathyreoidism. Before any medication:

E.A., a female, had an average of 85·6% of calcium excreted in the fæces.

E.B., a female, had an average of 92·1% of calcium excreted in the fæces.

Yet both these patients were in calcium equilibrium.

In the comparatively small series of normal patients studied by various workers, the percentage of fæcal calcium to the total calcium excreted varies over a wide range: from 52% to 94% on diets containing adequate calcium; from 46·6% to 95·6% on diets containing inadequate calcium. In hyperthyreoidism the range is from 52% to 85% with an adequate calcium intake; 32·3% to 56% with an inadequate calcium intake. Until a much larger series of both normal and pathological subjects has been studied, it will not be justifiable to draw conclusions, as Aub and Hunter have done, from the average excretion of calcium in the fæces, as to whether there is a special path for calcium excretion in hyperthyreoidism. There is no doubt that fæcal excretion of calcium is increased in hyperthyreoidism, because at times there is more calcium in the fæces than in the food. But there is, in general, a much greater relative change in urinary excretion, so that one is not justified in assuming that the augmented fæcal excretion of calcium in hyperthyreoidism constitutes a pathognomonic feature.

We have attempted to elucidate the problem of the excretory path of calcium in hyperthyreoidism by analysing the changes in our individual patients when they passed from their period of greatest negative calcium balance to a period of calcium equilibrium; in other words, we have made them act as their own controls. The data of four patients are available for analysis. (See Table A—Calcium and Phosphorus Excretion in Hyperthyreoidism.) In all, the change in urinary excretion was much greater than in fæcal excretion. Taking the excretion of calcium expressed as a percentage of the intake, we find that in changing from negative balance to equilibrium the urinary calcium falls 35%, 16%, 81·7% and 49·1% respectively in the four cases, while the fæcal calcium falls 14·3%, rises 10%, falls 17·1% and 19·5% respectively. One may conclude, therefore, that the calcium loss in hyperthyreoidism involves an augmented urinary and fæcal excretion, but has no special characteristics to distinguish it from similar losses in other pathological conditions associated with a negative calcium balance.

Phosphorus Excretion.

Sherman[101] states:

It must be kept clearly in mind that after *utilization* a large part of the phosphorus and a still larger part of the calcium is likely to be eliminated through the intestine instead of through the kidney.

Myers[46] states:

The elimination of calcium and phosphorus are interrelated, both as to the total excretion and path of elimination. An increased ingestion of either causes an increased elimination of the other at the expense of the body's store, if necessary. Proportionate increase in the intake of both increases the fæcal excretion.

Phosphorus Excretion in Normal Subjects. — Myers,[46] in a series of fourteen cases, found that an average of 34% of the excreted phosphorus appeared in the stool—range 23% to 45%. Sherman, Gillett and Pope,[105] with a phosphorus intake of 0·7 gramme a day, found 36·5% of the total output in the fæces. Sherman, Wheeler and Yates,[106] with a phosphorus intake of 0·68 gramme a day (Case I), found 23·7% of the total output in the fæces; with a phosphorus intake of 0·73 gramme a day (Case II), 28·8% of the total output was in the fæces. Bassett, Elden and McCann[14] found, Case Z 44·3%, Case S 35·2% of the total phosphorus output was in the fæces. In our normal cases, Gwen P. had 23·2% and Joan H. 41·4% of the total output of phosphorus in the fæces.

Phosphorus Excretion in Hyperthyreoidism.—In our hyperthyreoidic material, before any treatment other than rest in bed:

TABLE A.

Calcium and Phosphorus Excretion in Hyperthyreoidism. A comparison between the output of calcium and phosphorus in urine and stool during the stage of Maximum Negative Balance and the stage when Equilibrium was most nearly approached.

Subject.	Calcium.					Phosphorus.					
	Average Daily Intake in Grammes.	Average Daily Excretion.				Average Daily Intake in Grammes.	Average Daily Excretion.				
		Urine.		Stool.			Urine.		Stool.		
		Grammes.	Percentage of Intake.	Grammes.	Percentage of Intake.		Grammes.	Percentage of Intake.	Grammes.	Percentage of Intake.	
Albert I. ..	0·81	0·49	60·5	0·67	82·6	1·27	1·23	97·5	0·33	26·0	Whole of fore-period.(*a*)
	0·82	0·21	25·5	0·56	68·3	1·44	0·67	46·5	0·37	25·7	4th iodine period.(*b*)
Dorothy E.	0·773	0·356	46·0	0·813	105·0	1·20	1·01	84·2	0·42	35·0	Whole of fore-period.(*a*)
	0·650	0·195	30·0	0·750	115·0	1·11	0·695	62·6	0·44	39·6	4th and 6th iodine periods.(*b*)
Marjorie R.	0·55	0·534	97·1	0·579	105·3	0·981	0·708	72·2	0·416	42·4	Last 16 days of fore-period.(*a*)
	0·568	0·090	15·4	0·501	88·2	1·060	0·542	51·1	0·350	33·0	8th, 9th, 10th and 11th X ray periods.(*b*)
Darcia T.	0·611	0·430	70·4	0·577	96·7	1·229	1·034	84·1	0·311	25·3	Whole of fore-period.(*a*)
	0·609	0·130	21·3	0·471	77·2	1·073	0·733	68·3	0·217	20·2	Last nine periods.(*b*)

(*a*) Maximum negative balance. (*b*) Approximate equilibrium.

D.E.—average, 29·4% of the total output of phosphorus was in the stool.
J.McL.—average, 26·0% of the total output of phosphorus was in the stool.
A.I.—average, 21·2% of the total output of phosphorus was in the stool.
M.R.—average, 37·6% of the total output of phosphorus was in the stool.
D.T.—average, 23·1% of the total output of phosphorus was in the stool.
D.S.—average, 23·5% of the total output of phosphorus was in the stool.
P.W.—average, 29·6% of the total output of phosphorus was in the stool.

In our cases of hyperthyreoidism associated with hypoparathyreoidism, before treatment:

E.A.—average, 30% of the total output of phosphorus was in the stool.
E.B.—average, 39·7% of the total output of phosphorus was in the stool.

There is no relation between the path of calcium and of phosphorus excretion, but it is interesting to note that in patient D.S., who had the highest fæcal calcium, the fæcal phosphorus was low, while in patient M.R., who had the lowest fæcal calcium, the fæcal phosphorus was by far the highest.

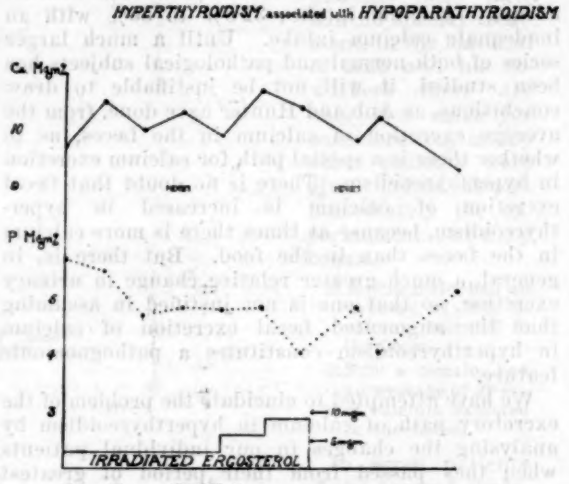
TABLE B.

Showing effect of the administration of vitamin D on calcium and phosphorus balance in patients suffering from chronic hyperthyreoidism associated with hypoparathyreoidism.

	Calcium. Grammes.	Phosphorus. Grammes.
Edith A.		
Average daily balance during fore-period	−0·029	+0·047
Average daily balance during administration of 3 cubic centimetres of "Radiostol" daily ..	+0·09	+0·111
Average daily balance during administration of 6 cubic centimetres of "Radiostol" daily ..	+0·089	+0·150
Average daily balance during administration of 9 cubic centimetres of "Radiostol" daily ..	+0·111	+0·158
Average daily balance after cessation of "Radiostol"	+0·177	+0·015
Emma B.		
Average daily balance during fore-period	−0·027	+0·037
Average daily balance during administration of 4 cubic centimetres of "Ostelin" daily ..	+0·013	+0·093

Analysing the changes in phosphorus excretion that take place in passing from the period of greatest negative balance to a period of equilibrium in individual cases (see Table A), we find that as in calcium excretion the greatest change is in the urine. Taking the excretion of phosphorus expressed as a percentage of the intake, we find that the urinary phosphorus falls 51·5%, 21·6%, 21·1% and 15·8% respectively, the fæcal phosphorus falls 0·3%, rises 2·8%, falls 7·7% and 4·7% respectively.

Changes Induced in Calcium and Phosphorus Excretion by the Menstrual Cycle.—In three of our patients menstruation seemed to cause a definite change in phosphorus excretion. In Case D.T. and Case W. there was an increased excretion coincident with the menstrual period; in Case E.A. the increase was immediately subsequent to the period. Menstruation did not cause any significant change in calcium excretion in any of our patients. Menstruation cannot be expected to produce changes of any magnitude in calcium and phosphorus balance, and in order to elicit any differences at all it would seem essential that the subject should be under absolutely standardized conditions, including rest in bed. We found no change in our normal patient G.P., but this subject was ambulant. Sherman and his co-workers[105][102][106] found that the menstrual cycle had no effect on calcium and phosphorus excretion in normal subjects. Their subjects were ambulant, and the calcium and phosphorus in the food was calculated and not estimated, so that small changes could easily have been masked by changes in the actual calcium and phosphorus intake.



GRAPH 12 EDITH A.
Showing the changes in SERUM CALCIUM and INORGANIC PHOSPHORUS, before, during, and after the administration of IRRADIATED ERGOSTEROL.

GRAPH XII.

General Discussion.

The excessive mobilization and excretion of calcium and phosphorus in patients suffering from hyperthyreoidism are due either to the increased production of thyroxin or to an associated hyperparathyreoidism. Other possible causes have been investigated and excluded by the researches of the Boston School. If the increased circulating thyroxin has "a direct stimulating catabolic effect on the calcium deposits in the bones", it should be possible to discover some direct relationship between the amount of calcium mobilized and the amount of circulating thyroxin as measured by the basal metabolism. Though the amount of calcium mobilized need not be proportional to the basal metabolic rate, it should be of comparable extent in patients of the same approximate age, sex and body weight who have the same degree of hyperthyreoidism; the amount of calcium mobilized should vary directly with changes in the basal metabolism of the individual; and calcium mobilization should be a constant finding in all cases of hyperthyreoidism. On the other hand, if an associated hyperparathyreoidism is the cause of the anomalies in calcium and phosphorus metabolism, a direct relationship between the amount of calcium mobilized and the degree of hyperthyreoidism would

not be necessary, and the amount of calcium and phosphorus mobilized could vary independently of the basal metabolism. Our evidence is strongly in favour of an associated hyperparathyreoidism.

In the experimental data presented, two subjects were treated solely with iodine. Of these, Albert I. showed a direct relationship between the level of the basal metabolism and the amount of calcium and phosphorus lost from the body. During the fore-period when the metabolism was raised there was a definitely negative calcium and phosphorus balance; during the iodine therapy when the metabolism fell the calcium and phosphorus balance approached equilibrium. The second subject, Dorothy E., did not show this relationship, and we find the metabolism remaining at a constant level while the calcium and phosphorus losses are increasing. The next patient, Darcia T., who was treated with iodine and then had therapeutic X rays, began with a definitely elevated metabolism and a markedly negative calcium balance. On iodine therapy the metabolism fell and the calcium and phosphorus balances approached equilibrium, but later the metabolism rose steadily to a level definitely above the initial level, while the calcium and phosphorus balance approached nearer to equilibrium and actually became definitely positive at the time when the metabolism was at its highest recorded level. An inspection of the protocols shows that during the fore-period the basal metabolic rate ranged between +36% and +20%; the calcium balance was −0·4 gramme daily, the phosphorus balance −0·112 gramme daily. During the twentieth period, the basal metabolic rate was +43%, the calcium balance was +0·06 gramme daily, and the phosphorus balance +0·135 gramme daily.

The results of the next patient, Majorie R., who was treated with therapeutic X rays and then had iodine, show still more definitely that the factors controlling the basal metabolism and the balance of calcium and phosphorus are quite independent. In this patient the X rays were practically without effect on the level of heat production, while the balances of both calcium and phosphorus, from being severely negative, became markedly positive. It seems to us that the only logical conclusion to be drawn was that the X rays had no definite effect on the thyreoid gland, but caused a marked depression in the activity of the parathyreoid glands. Otherwise we should have to allow that thyroxin has the unique physiological function of being able at the same concentration in the blood to cause either a profound loss, equilibrium or a marked storage of calcium and phosphorus.

The results of the experiments on Phyllis W. illustrate in another way the lack of relationship between the amount of circulating thyroxin and the amount of calcium and phosphorus mobilized. During the fore-period there was only a moderately negative calcium and phosphorus balance, but following X ray therapy the calcium and phosphorus loss increased a hundredfold, though the basal metabolism was lower.

The experimental results obtained in the case of Dulcie S. show that calcium and phosphorus equilibrium can be present in spite of severe hyperthyreoidism. The basal metabolism of this patient, during the fore-period, was constantly in the vicinity of +60%, yet the loss of calcium (0·04 gramme *per diem*) was not greater than in one of our normal controls, and the loss of phosphorus (0·17 gramme *per diem*) not appreciably greater than that of one of the normal controls. During the course of study the metabolism fell from +67% to −1%, yet the calcium balance was hardly affected, and never became positive in spite of an urgent need for calcium. At one stage of the experiment the calcium loss was increasing though the basal metabolic rate was steadily falling.

In our next patient, Jean McL., who was treated with deep X rays, the basal metabolism remained remarkably constant while the negative calcium balance increased from 0·39 gramme *per diem* (average of fore-period) to 0·561 gramme *per diem* (average of X ray period). Taking all the data of this patient into consideration, it is difficult not to conclude that the X rays had no appreciable effect on the thyreoid gland, but stimulated the already hyperfunctioning parathyreoid glands.

Lastly, the two patients, Edith A. and Emma B., who had a hypoparathyreoidism associated with hyperthyreoidism, and who were in calcium and phosphorus equilibrium, provide the final link in the evidence that hyperthyreoidism *per se* has no specific effect on calcium and phosphorus metabolism.

The amount of calcium and phosphorus mobilized and excreted is therefore determined by the degree of hyperparathyreoidism present, and indeed can be used as a measure of the extent of parathyreoid stimulation. The amount of hyperparathyreoidism has been shown to vary in different patients and in the same patient from time to time; if for any reason the parathyreoid glands cannot or do not become hyperplastic there will be no increased loss of calcium and phosphorus from the body.

A priori it would not be unexpected to find hyperparathyreoidism frequently associated with hyperthyreoidism. The greatly increased vascularity of the hyperplastic thyreoid gland may lead to a slight local rise in temperature which would stimulate the adjacent tissues; in exceptional cases where the parathyreoid glands are in abnormal positions they may escape this stimulus. More important would be the effect of the catalytic action of the increased circulation of thyroxin, which would be expected to stimulate the parathyreoid glands in general with all tissue activities. It is not necessary to assume that hyperparathyreoidism should be inevitable, as combinations of endocrine imbalance are notoriously bizarre.

The response of the parathyreoid glands to radiation was variable. We consider that they were depressed in two subjects, Darcia T. and Marjorie R., and stimulated in three, Dulcie S., Phyllis W. and Jean McL. The response of the thyreoid gland to radiation is also variable, and when we consider

that there is no means of controlling the actual dose that reaches the parathyreoid glands, owing to variation in their number and position and to the variable amount of thyreoid tissue to be penetrated, such variations would be expected. On the whole the parathyreoid glands appear to be very sensitive to radiation.

The experimental results showed that if hyperthyreoidic patients receive a diet that satisfies the special requirements of the hyperthyreoidic state, the mobilized calcium and phosphorus are excreted in a similar manner to that obtaining in other diseases associated with a negative calcium and phosphorus balance.

Conclusions.

1. The thesis of Aub and his co-workers and of Hunter that thyroxin has a direct catabolic effect on the calcium deposits in the bones cannot be accepted on the evidence they present.

2. Seven patients suffering from hyperthyreoidism have been carefully studied. An analysis of their experimental data provides definite evidence in favour of an associated hyperparathyreoidism being the direct cause of the excessive mobilization and excretion of calcium and phosphorus.

3. Two patients suffering from hyperthyreoidism with an associated hypoparathyreoidism were studied. Both patients were in calcium and phosphorus equilibrium.

4. Though hyperthyreoidism is frequently accompanied by a negative calcium and phosphorus balance, it is not invariably so. It is possible for calcium and phosphorus equilibrium or a positive calcium and phosphorus balance to be present.

5. Hyperthyreoidism *per se* has no specific effect on calcium and phosphorus metabolism.

6. We were unable to confirm the findings of Aub and his co-workers and of Hunter that the excretion of the mobilized calcium is predominantly fæcal.

(Part II of this paper will appear in next week's issue.)

Reviews.

THE STORY OF SURGERY.

For the series of short medical histories published by John Bale, Sons and Danielsson, Sir D'Arcy Power has written a brief but interesting history of surgery. The book, within its ninety pages, gives a bird's eye view of the progress made by the surgical art from the days of ancient Egypt to the present time.

The pages on Egyptian surgery give a *résumé* of the Edwin Smith surgical papyrus, which, while it was discovered in 1872, was not deciphered and translated until 1922. This papyrus is the work of a skilled surgeon who had seen war service and has given us quite a new outlook on the surgery of the ancient Egyptians. The surgeon, amongst other modern ideas, used splints of wood or linen soaked in glue or impregnated with plaster, and brought his wounds together with adhesive plaster.

A description is given of the surgical renaissance which began in southern Italy about the year one thousand; and we have short accounts, amongst others, of William of Saliceto (1201-1277), who was far in advance of the surgeons of five hundred years later, in that he taught that wounds need not suppurate, for he used simple dressings of white of egg instead of ointments. Surgeons in those days did not enjoy a very good reputation, for William says that "a wise surgeon will refrain from stealing whilst he is actually in attendance upon a patient". All these mediæval surgeons endeavoured to get their wounds to heal by first intention, and it is difficult to understand how the doctrine of "pus laudabile" first arose and became an accepted tenet until the days of Lister. Henri de Mondeville (1260-1320) tells us: "If they are treated on Theodoric's and my instructions every wound will heal without pus. Many more surgeons know how to cause suppuration than how to heal a wound."

Guy de Chauliac, the great French surgeon, whose "Chirurgia Magna" influenced the surgery of Europe for centuries, made a retrograde step when he advised the use of ointments in the healing of wounds.

We are told about John Arderne, the first of the great English surgeons, and how he became famous for his operation on fistula.

The formation of the various guilds and corporations of surgeons and barbers to prevent the profession from becoming a mere trade and to raise the status and qualifications of the surgeon is fully detailed.

The English surgeons of the Tudor and Stuart periods provide one of the most fascinating chapters in the book, and the quotations given from their works make us realize that our contemporary surgeons, while they have gained greatly in surgical knowledge, have fallen away in literary charm since the days of their Elizabethan colleagues.

The great army surgeons, Jerome of Brunswick (1450-1533), Hans von Gersdorff, John of Vigo, and the greatest of all, Ambroise Paré (1510-1590), live again in these pages; and Sir D'Arcy Power tells us in quotations from their works how these brave men helped the wounded and advanced the art of surgery.

With the foundation of infirmaries in England in the eighteenth century surgery began a new era, and whereas formerly a surgeon obtained his training in war, there now came into existence a succession of men trained in civil practice.

William Cheselden (1688-1752), who performed lithotomy in twenty-four seconds, and who was a man of education and the friend of Mead and Pope, did much to raise the status of his calling. Percival Pott (1713-1788) consolidated the social position made by Cheselden and enabled the surgeon to be looked upon as the equal of the physician.

The era of scientific surgery began in London with William and John Hunter in 1741; and their pupils, Cline, Abernethy, Astley Cooper, by studying surgical pathology and anatomy, cleared the way for Sir William Lawrence and Sir James Paget and led up to the days of Lister.

A chapter each is devoted to war surgery, anæsthesia and surgical nursing, and one is filled with admiration at the amount of historical information compressed into this small book.

It would be well if every surgeon purchased a copy of this little book and read it well, if only to realize that surgery did not begin with Lister. We are reminded of this by the words of old Thomas Fuller, so often quoted by Sir William Osler: "For this world affordeth no new accidents. Old accidents return again, furbished over with some new and different circumstances."

[1] "A Short History of Surgery", by Sir D'A. Power, K.B.E., F.R.C.S.; 1933. London: John Bale, Sons and Danielsson. Crown 8vo., pp. 91. Price 3s. 6d. net.

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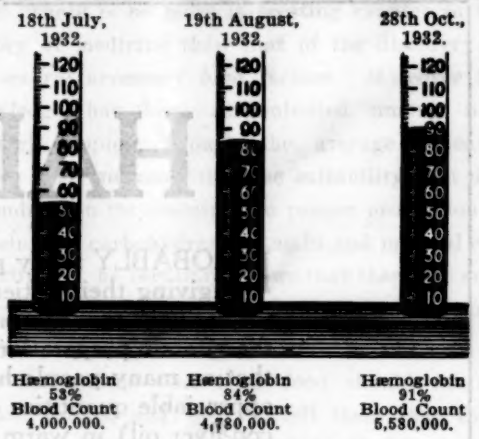

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NUTRITION.

"OUR scientific knowledge stands far ahead of our practice." These words are used by Sir George Newman, Chief Medical Officer of the Ministry of Health of Great Britain, when he discusses the relation of food to health and disease in his annual report for 1932. They are at once a reproach and a challenge. They might, of course, be used in regard to many subjects in medicine other than nutrition.

Man in his primitive state lived a hand to mouth existence. He knew nothing of the conservation or storage of food. His weakly or unwanted children often died of exposure and when he became ill or enfeebled by age he received scant consideration from his fellows. But for all his lack of knowledge, the savage was often a fine specimen of manhood, capable of endurance, and in virtue of his prowess, worthy of admiration. With the growth of culture, of so-called civilization, life became easier; food became more plentiful and men learned to adapt it to their requirements. At the same time history shows that until comparatively recent times there was an appalling wastage of life, particularly among those of tender years, and that most of the deaths occurred because nutrition in infancy and childhood was not understood. The growth of knowledge of food values and of the constituents of a diet necessary to health is of comparatively recent date. There is no more interesting chapter in the history of medicine than that of the discovery of the several accessory food factors. Moreover the knowledge has been disseminated among non-medical people. Though the average educated person may not know that the suitability of a diet depends upon its containing a proper proportion of protein, fat, carbohydrate, vitamin and mineral salt constituents, he certainly knows that there are such things as vitamins and that his food should contain them.

To tell people that their food should contain certain things, and even to tell them that these things should be present in their diet in certain proportions is not sufficient. Much more is needed. Perhaps first of all mention should be made of the cooking of food. Very few people know how to cook food properly. The human stomach is a long-suffering structure; it brooks many insults and suffers many privations. Were it more easily provoked to rebellion, many of those who are ceded the title of cook would have to make an effort to justify the name. The practice adopted in certain schools of teaching cooking to girls should be extended; and incidentally medical students should be taught that there is an art in cooking, even if they are not taught how to prepare some of the special foods that they will later on order for their patients. In addition to the cooking of food, its cost and availability have to be considered. It is little use telling an Australian working man who is on the basic wage and who has a large family of children that he and his dependants should, for example, eat more fruit when fruit is sold only at prices which are ridiculously high for a country producing it in abundance. A third factor to be remembered is the requirement of the individual body—the requirement in regard to growth, repair and energy. The requirements of a child are different from the requirements of an adult; and the requirements of a man in a sedentary occupation are vastly different from those of one who earns his living by manual labour. Lastly, the physiological condition of the body has to be taken into

consideration. Food will be of benefit to the body only if the mastication, the processes of digestion and excretion are normal. Sir George Newman sums up the matter well by pointing out that nutrition, like malnutrition, is a process. He writes:

> In endeavouring to estimate the degree of nutrition of a human body we must not think only, or mainly, of its bulk or weight, but of ratio of stature to weight; of the general appearance, and "substance" of the body; of its carriage and bearing and suppleness; of the firmness of tissues and the development of the muscular system; of the condition of the skin and the redness of the mucous membranes; of the nervous system as expressed in listlessness or alertness, apathy or keenness; of the relative balance and co-ordination of the functions and powers of the body; and of its capacity and power of work.

We recognize living as an art—we speak, perhaps glibly, of the art of living. The life of the body is but part of the life of man. Man will be able to live his life to the full only if the life of the body is clean and healthy. The body can be clean and healthy only if it is properly nourished. This brings us back to Sir George Newman's statement that our scientific knowledge is far ahead of our practice. It is the duty of the medical practitioner to see that human bodies are well nourished. Curative medicine is concerned with the body in malnutrition; preventive medicine, the more important aspect of medicine, is directed to the nutrition of the body that it may be kept in health. Medical practitioners notoriously pay far too little attention to the nutrition, the diet, of the body in disease; they pay less to the care of the body not affected by disease. They have the knowledge and should continually remind themselves that scientific knowledge is useless unless it is applied in practice.

Current Comment.

CAVITIES IN THE LUNGS.

CONSIDERABLE interest has been taken of recent years in the question of the pulmonary cavity. Bronchiectatic cavities do not appear to be essentially very dangerous *per se*, but once they are infected, as they almost invariably are, they become septic wells, obnoxious, pervasive and destructive. Tuberculous cavities are the aftermath of the caseation and breaking down of lung tissue; they invite hæmoptysis and extension of infective processes both by the tubercle bacillus and other bacteria. Moreover, they are the heralds of decline, and the mournful experience of the clinician and radiologist is that advancing cavitation spells a bad prognosis.

As regards bronchiectasis, the weight of opinion is against collapse therapy as a successful means of treatment. But this, as its protagonists point out, is often due to the fact that treatment is started too late, when the process is bilateral and extensive. E. Rist, of Paris, in addressing the American College of Physicians, points out the dangers of anaerobic infection in bronchiectasis.[1] He claims that it is our duty to give a trial to any means that may promise a reasonable chance of success. In his address he does not damp our optimism by referring to the frequent occurrence of bilateral lesions (though in several of his unsuccessful cases bilateral cavities were present), but he remarks that the fear of pleural adhesions need be no deterrent, as these constitute a serious difficulty less often than is usually supposed. He claims that a number of patients remained well for varying periods of years after suspension of the collapse treatment. Though much has been written lately anent the supposed uselessness of such measures in this serious and disabling disease, it might be well for those interested not to dismiss this matter lightly. Lobectomy, the surgical ideal, is not often applicable, nor is it immediately practicable in this relatively small and scattered population. It would seem to be reasonable to bear in mind the possible value of artificial pneumothorax in specially selected cases. Rist does not claim that the cavities are permanently obliterated. He believes that collapse favours efficient bronchial drainage and thus paves the way for healing of the bronchopneumonic infection.

The other type of pulmonary cavity, the tuberculous, is even more important. E. C. Janes, in writing of the surgical obliteration of cavities in the lungs, sums up the position by saying that "the treatment of chronic fibroid phthisis practically resolves itself into the treatment of the pulmonary cavity".[2] This is, of course, a slightly exaggerated statement, but it is essentially true, as all forms of tuberculous infiltration of the lung at least tend to cavitate, and in so doing introduce a graver prognostic element into the patient's condition. Janes further points out that cavities are incompatible with long life in the average patient. This is certainly true. Everyone can think of examples of longevity among the subjects of chronic fibrocaseous tuberculosis, but these are but few. Too often, on the contrary, these patients, after early improvement under good conditions, tend to relapse, and the newly invigorated disease proceeds apace. Sanatorium treatment is often misunderstood in the handling of the tuberculous patient. It starts him on a new career, guides and directs him, teaches him to care for himself and others, but it cannot be expected always to reverse a process that is alike destructive and relentless. Further, the cavity always means sputum, and usually infective sputum.

[1] *Annals of Internal Medicine*, October, 1933.
[2] *Canadian Medical Association Journal*, October, 1933.

The transcendent importance of this from the point of view of public health needs no further comment. After all, it is only the old story, that any intelligent treatment of a disease must be based upon an intelligent understanding of its pathology. Therefore physicians and hygienists must be, as it were, "cavity-conscious" in the handling of this problem. Surgeons should be included also, for surgical measures are being more widely adopted of late years. Janes reviews briefly the now well known methods of causing pulmonary collapse. Artificial pneumothorax is, of course, the method of choice. Unfortunately many patients have advanced disease before treatment is begun, and often before a diagnosis is made. When disease is bilateral little can be done in the direction of direct control of the diseased areas. But when unilateral disease exists and the lung is adherent, obliteration of cavities may still be accomplished by the severing of the adhesions that moor the cavitated areas to the chest wall. If this is not possible, there remains the operation of thoracoplasty. An adjuvant procedure is evulsion of the phrenic nerve. These subjects have been fully described in this journal by various physicians and surgeons of experience.

The articles here summarized do not introduce any new idea or concept into the subject of pulmonary disease. But they point a moral. Every medical practitioner who sees a patient with acute appendicitis naturally has the vision of an abscess before his mental eye; a rheumatic carditis summons up the spectre of a fibrillating and failing heart; so should pulmonary disease, bronchiectatic and tuberculous, be associated with the picture of cavitation with all its attendant evils.

MONILIASIS.

FUNGUS infections have in recent years assumed a greater importance. A certain languid interest was once all that could be invoked in their study, and probably many practitioners encountered local infections due to fungi without realizing their nature. Thus, thrush in the mouth is a household word, but even now it is not generally recognized that vaginal infection due to the same cause, especially during pregnancy, is not rare. Infections of the nails by fungi are not uncommon; also of the feet and other parts of the body. Many will remember, too, the remarkable plague of field mice that invaded many country districts about fifteen years ago, spreading in its train a severe and rather intractable fungus infection, especially of the scalp, where it caused in many cases the state known as kerion, not so frequently seen in these parts. But though we are becoming more educated with regard to this group of infections, it should be borne in mind that there are possibilities of systemic invasion by certain of the fungi. Attention has been drawn to them in these pages.

Lawrence W. Smith and Machteld E. Sano have described a case of moniliasis with meningeal involvement.[1] This is apparently unique in the literature, though other fungus infections of the central neural membranes have been described here and elsewhere. The patient was a baby aged twenty-two months. He had been ill for a fortnight with fever and cough when he was seen by a physician who found a white membrane in the mouth and throat. This was patchy, and smears revealed an organism with the characters of oidium or monilia. There were present the signs of a bronchopneumonia. Lumbar puncture revealed clear fluid under increased pressure, with two cells to the cubic millimetre. On culture a fungus was grown identical with that found in the mouth. For some days there was improvement and the membranous inflammation of the pharynx was subsiding, but the pulmonary condition became worse and bilateral *otitis media* developed. Culture of laryngeal swabs and of the blood revealed streptococci, but the former showed also a dominating growth of monilia. Death occurred some days later, being heralded by the appearance of strabismus and the occurrence of convulsions. Autopsy revealed the usual changes of bronchopneumonia in the lungs, some inflammation of the mucosa of the alimentary tract, and an acute purulent meningitis. *Post mortem* culture of the blood yielded streptococci and monilia, and the latter was also grown from the throat, alimentary tract and spinal fluid.

Here, then, we have the rare event of a thrush infection spreading rapidly in a young child. Invasion of the lungs took place by this and other secondary organisms; blood stream infection occurred, and an apparently terminal localization in the meninges. The child was rickety and poorly nourished; this doubtless favoured and hastened both onset and course of infection.

Bacteriological investigation was carried out on the cultured organisms and the effects on rabbits observed both in the case of this strain and other allied strains of monilia. One curious and interesting feature was the apparently selective nature of the fungus for the central nervous system of the experimental animals. Not only was the monilia isolated from this patient pathogenic for the rabbit, but lesions were found in the brain and meninges. The cerebellum was particularly affected, and the right side especially. It is suggested that this strain has an affinity for neural tissue, as such phenomena were but seldom, if ever, observed with other strains. The production of a meningitis was almost a constant feature in the animal experiments, which is interesting in view of the clinical history of the patient. This is an example of a rare case that is instructive, for it shows that the general lessons of bacteriology as regards pathenogenicity of organisms hold for the higher bacterial forms also. In other words, however innocent an infecting agent may appear to be, it may at times assume an unlooked for virulence. This may apparently occur even in the case of such a simple malady as thrush.

[1] *The Journal of Infectious Diseases*, September-October, 1933.

Abstracts from Current Medical Literature.

GYNÆCOLOGY.

Hormonic Factors Controlling the Functional Activity of the Uterus.

J. M. ROBSON (*Journal of Obstetrics and Gynæcology of the British Empire*, May, 1933) carried out experiments to determine the hormonic influence on the activity of the uterus. He found that during the early stages of gestation only large doses of oxytocic hormones had any effect on the uterine muscle; on the other hand, the vasopressin hormone always caused a contraction, even in those cases in which oxytocin failed to elicit a response. As pregnancy progressed, the necessary dose of the oxytocin became less, and at parturition reactivity of the uterus to oxytocin reached its maximum. The action of ergotoxin followed along similar lines, with practically no action in the earlier months. In the *corpus luteum* there appear to be two definite substances, one which may be termed the inhibitory hormone and the other a progestational one; it has been shown that both these actions are dependent upon the presence of œsterin, which appears to sensitize the tissues to their action. In a human subject who has previously been treated with œsterin the luteal hormone causes a typical premenstrual condition of the endometrium and leads to menstruation. If reaction of the uterus to a hormone plays an essential part in controlling pregnancy and parturition, it must, after the earliest stages, be developed independently of the *corpus luteum*, and the gradually increasing reactivity of the uterus as pregnancy proceeds to term cannot be merely due to the withdrawal of the luteal secretion. It is suggested by the author that this reactivity is result of the increased production of œsterin, which can take place even after the removal of the ovaries.

Ovarian Dysfunction.

JAMES ROBERT GOODALL (*The Journal of Obstetrics and Gynæcology of the British Empire*, June, 1933) has contributed his observations on some aspects of ovarian dysfunction. He briefly reviews the subject of ovarian and uterine physiology in the light of modern knowledge. After referring to the three factors (ovulation, folliculin and lutein) which are considered to be the means by which the ovary exerts its control in the female body, he discusses the relation between the ovary, the anterior pituitary, the thyreoid and suprarenals. When there is a general instability of all the glands of internal secretions we have a condition frequently spoken of as glandular "imbalance". From this group of cases are a majority of women who have been regarded as neurasthenic and asthenic and who seem to be increasing in number with the increasing strain of modern life. They may express themselves in syndromes, which may be either cardiac, vasomotor, cerebral, pelvic, enteric or locomotor. In each of these groups the symptoms are referable to the particular system. Endocrine treatment in general has failed to control these conditions. The author pleads for a more careful examination of each patient, both symptomatically and physically. He requires, first, a detail history; secondly, a complete physical examination, under anæsthesia if necessary; and thirdly, a complete knowledge as possible of the attributes of the endocrine glands. At the same time he points out that in adolescence many of these symptoms are modified to a considerable extent and require special study for recognition. Each research laboratory gives a different name to its own product, which results in great confusion in the minds of clinicians, but there are really four groups: (i) Those with the properties of the Graafian follicle —folliculin, memformem, theelin *et cetera*; (ii) those that possess the properties of the lutein secretion—progestin, and the mostly inert commercial *corpus luteum* products; (iii) those with anterior pituitary properties—anterior pituitary-like substances obtained from placentas and from the urine of pregnant women, such as "A.P.L.", "Antuitrin S.", Zondek's prolan *et cetera*; (iv) impure or mixed compounds, mostly with anterior pituitary properties—emmenin, antuitrin, and the many commercially prepared compound tablets. In primary amenorrhœa the author considers that the prominent cause is that of primary hypo-anterior-pituitary origin, and the ovary and thyreoid are secondarily involved in the dyscrasia. The treatment indicated would therefore be anterior pituitrin reinforced with ovarian extract of various kinds. In sterility the common cause is hypothyreoidism. The treatment is by ovarian hormone or pituitary extract or a combination of both. In ovarian dysmenorrhœa, which is usually premenstrual, bilateral, boring in character, and referred to the lower quadrants, and radiating down the legs and relieved by the complete onset of the menstrual flow, the condition is rarely, if ever, primarily functional in origin. The true functional dysmenorrhœa is the so-called uterine type—cramp-like, intermittent pains, like labour pains, coming on the first day of the flow, felt low in the mid-abdomen, relieved by a free menstrual discharge, characteristically common in young girls, seldom in parous women; relieved by parity and often by marriage. The latter type responds well to endocrine treatment. In menorrhagia of endocrine origin the disturbance may be due to lack of cooperation between the follicular hormone and the *corpus luteum*. This is frequently overcome by giving anterior pituitary extract. In every case, of course, pathological conditions of the ovary must be excluded. In many cases the uterine hæmorrhage is an expression of a low basal metabolic rate, the correction of which arrests the bleeding. In other instances, owing to the combination of the two glands, the pituitary and thyreoid being in mutual distress, a combination of extracts is most efficient. In calcium metabolic deficiency, parathormone and calcium are indicated. In women approaching the menopause more adequate methods of treatment by operation, radium or X rays may be necessary.

Ovariotomy.

HERBERT R. SPENCER (*Proceedings of the Royal Society of Medicine*, September, 1933) has published a review of a consecutive series of 658 ovariotomies extending over forty years of practical work. The ovariotomies were bilateral in 164 cases, on the right side in 250, on the left in 238. In some of the unilateral cases the other ovary had been or was subsequently removed for a similar or different growth. Sixty-three of the tumours complicated pregnancy, labour or the puerperium. The youngest patient in the series was aged fourteen, the eldest eighty-two. Eleven were over seventy years of age. Adhesions were present in over two-thirds of the whole number of cases. The most frequent of the adhesions were to the abdominal wall and omentum. In 85 the pedicle of the tumour was twisted. Twelve tumours had been tapped before operation. The author holds that, except in very rare circumstances, tapping should have no place in modern practice. Forty-one tumours were ruptured before operation; seven of these were malignant. Thirty-three benign ovarian cysts contained a papilloma inside and some outside the cyst. In addition, seventeen malignant cysts were "papillomatous". Sixty-six tumours were dermoid. There were twenty ovarian fibroids in the series, eighteen of which were fibromata and two adenofibromata. There were 45 parovarian tumours, 19 occurring in single patients and 26 in married women who had had in all 36 children. There were 58 suppurating tumours, one was a parovarian cyst communicating with the descending colon. There were 67 malignant tumours, of which 66 were malignant ovarian tumours and one a benign unilocular cyst with cancer of the body of the uterus. Fifty-eight of the 66 were carcinomata, six sarcomata, and two endotheliomata. All the parovarian cysts were benign. The frequency of malignant disease in the author's series is just over 10%. He is of opinion that the high frequency of malignancy in ovarian tumours, often stated as from 20% to 25%, is exaggerated, and that the error is due to mistaking benign for malignant papilloma and fibroma for sarcoma. Thirty-five patients died after opera-

tion. The author concludes by stating his opinion, based on his own experience, that all benign ovarian tumours, however adherent and whether papillomatous or not, can and should be removed. Some of the benign papillomatous tumours closely resemble malignant growths. If a patient with such a tumour, thought to be malignant, is found two years after an exploratory operation to be fairly well, the surgeon should conclude that he has made a mistake and should remove the tumour. The author advocates the removal of malignant tumours, even in the presence of accessible secondary growths, if the condition of the patient will allow. He reports some results showing the value of X rays and radium in curing or checking metastatic growths.

OBSTETRICS.

Forceps Delivery.

R. WILL (*Monatsschrift für Geburtshülfe und Gynäkologie*, November, 1932) has analysed the cases of forceps delivery occurring at the Leipzig clinic over a five-year period. There were 16,242 births with 728 forceps deliveries (4·48%). Four-fifths of the cases occurred with *primigravidæ*, and the lessening number of *multiparæ* was believed to be due to the marked lowering of the birth rate within recent years. Four maternal deaths were noted due to puerperal sepsis, pulmonary embolism, and two from acute circulatory failure. The fœtal mortality was 10·85%. The author states that male children more frequently required forceps extraction because of the larger size of their heads. The effect of age was also interesting: Women over forty years of age had a rate five times that of the twenty-five to twenty-nine years group and ten times that of young *primigravidæ* under twenty years. Maternal indications for the use of forceps largely outweighed those of fœtal origin. The article is profusely illustrated with tables summarizing the author's findings.

A Study of Ureteral Tone During Pregnancy.

D. BAIRD (*Journal of Obstetrics and Gynæcology of the British Empire*, May, 1933) investigates the tone of the ureter at different stages of pregnancy. By means of a ureteral catheter connected to a water manometer he was able to demonstrate that the factors in the production of renal stasis are: (*a*) tone of the ureter, (*b*) pressure of the uterus on the ureter at the pelvic brim. The latter was more marked in *primiparæ* owing to the stronger abdominal walls. The pressure of the uterus is an ever-increasing one, so that the decrease in stasis which takes place near term must depend on improvement in ureteral tone, and this is found to occur. A distinct lowering of tone was noted in the puerperium. Clinical experience shows that pyelitis is more common between the fourth and sixth months of pregnancy and is also more common in *primiparæ*. The experimental results go to show that ureteral tone is at its lowest at this period, and pressure on the ureter is greater in *primiparæ* than in *multiparæ*. It was also found that by putting a patient on her side or in the knee-chest position urine would flow past the obstruction at the brim owing to the relief of pressure of the uterus.

Anæmia of Pregnancy.

W. SCHULTZ (*Münchener Medizinische Wochenschrift*, May 5, 1933) investigated 567 pregnant women and found that in half of these the hæmoglobin was reduced by 10% as compared with the normal woman. This diminished hæmoglobin is only apparent since the volume of blood is increased during pregnancy. True pregnancy anæmia (hæmoglobin less than 60%, red blood cells less than 3,000,000 per cubic millimetre) is very rare, for the author saw only 3% of patients affected. Some of these patients were anæmic before pregnancy; to that anæmia are added the blood changes of pregnancy; the result will be a very severe anæmia. Therapeutically this anæmia responds well to iron. In thirteen years the author saw only four cases of pernicious type of anæmia in pregnancy.

The Sex of the Fœtus.

JULIUS MANGER (*Deutsche Medizinische Wochenschrift*, June 9, 1933) states that the fact that follicular hormone may have an effect on the growth of plants induced him to make efforts to discover whether the sex of the expected child could be discovered from the action of the urine of pregnant women on germinating seeds of barley or wheat. The result of this work showed that quicker growth of the barley as compared with wheat denoted a girl, whilst no increased or delayed growth denoted a boy. In 100 pregnant women 80% of the diagnoses were correct and 20% were false.

The Effects of Intravenous Injections of Hypertonic Glucose Solution.

V. P. MAZZOLA AND M. H. TORREY (*American Journal of Obstetrics and Gynecology*, May, 1933) have carried out experiments on the cat to determine the pulse pressure, blood pressure and pulse rate. The method adopted was to insert a carotid cannula and connect it to a mercury manometer. This procedure was carried out under "Sodium amytal" anæsthesia. The results obtained showed that the rate of infusion of 50% glucose into the vein seemed to be a factor which determined the blood pressure response. When the rate of infusion was fast, 8·5 cubic centimetres per minute, there were three definite stages. The first was a rise lasting a few seconds. The second was a temporary fall, which depended on the amount and the rate—the greater the amount, the greater the fall, and this also applied to the rate. The third stage was a steady rise in both pulse and blood pressure. These experiments were also carried out on cats which had previously suffered a loss of blood. The conclusions reached were: (i) that 50% glucose injected intravenously into cats with a reduced blood pressure produced a final sustained rise in blood pressure; (ii) it caused sustained rise in pulse pressure; (iii) it produced sustained reduction in pulse rate, and slow injection was preferred to rapid. It was noted that pre-operative injection of 50% glucose solution diminished the fall in blood pressure due to hæmorrhage.

Diabetes in Pregnancy.

J. RONSHEIM (*American Journal of Obstetrics and Gynecology*, May, 1933) found in the records of the Jewish Hospital since 1920, thirty-six cases of pregnancy complicated by diabetes. These statistics are not concerned with those who have only lactose in their urine, nor with those in whom the sugar in the urine is due to a low sugar threshold, the so-called renal diabetes. The author divides the condition into three groups: the diabetic who becomes pregnant, the pregnant woman who develops diabetes, and the pregnant woman who at no time shows any evidence of diabetes, but in whom, after a catastrophe has beset the pregnancy, evidence of a latent diabetes is established by her response to the sugar tolerance test. The last mentioned type is a real menace to the unborn child, because the condition is unsuspected and death of the fœtus may result in a premature labour or death of the fœtus may occur some weeks before term. Before the use of insulin the maternal mortality was from 15% to 30%. The lessening of fœtal mortality has not shown a correspondence; in addition, the deaths from prematurity and monstrosities must also be added. The author is of the opinion that in view of the patients tending to have large babies and the likelihood of death of the fœtus in the last three weeks, Cæsarean section under spinal anæsthesia best serves the interest of patient and baby. The induction of labour with increased risk of sepsis appears to be contraindicated. In cases of recurrent miscarriages or still-births without determinable cause, the sugar tolerance test may indicate that the patient is a potential diabetic.

H. J. STANDER, in discussing this paper in the same journal, disagrees with the desirability of Cæsarean section in diabetes because he is of the opinion that although insulin has done a great deal, the diabetic patient is not quite suitable for Cæsarean section, and especially with the results as to the chance of monstrosities *et cetera*.

Special Articles on Treatment.

(Contributed by request.)

XXIV.

ANTE-NATAL TREATMENT OF THE TOXÆMIAS OF PREGNANCY.

The Toxæmias of Early Pregnancy.

APART from some minor conditions which are now regarded as probably of toxæmic origin, the toxæmia of early pregnancy which occasions anxiety is that manifested as grave or pernicious vomiting.

Hyperemesis Gravidarum.

The vomiting of pregnancy is usually classified as:

1. Associated, that is, the vomiting is due to some other lesion, such as gastric ulcer or carcinoma, cerebral tumour, *tabes dorsalis et cetera*. This associated vomiting may be aggravated by the coincidental gestation, but it cannot justly be regarded as due to toxæmia of pregnancy.

2. Reflex vomiting, said to be due to the presence of minor pelvic pathological conditions, such as retroversion, erosion of the cervix. The influence of these conditions is today very much discounted, and the good effect of procedures for their correction is probably more psychological than physical.

3. Neurotic vomiting. It is doubtful if there is any such thing as pure neurotic vomiting of pregnancy. It is true that the sickness is accentuated by the effects of bad environment, unwise domestic solicitude or neglect, impressions produced by the pernicious chatter of relatives and by the morbid and impertinent interest of neighbours in the health of young brides, but there is probably a toxæmic factor in all such cases.

4. Toxæmic vomiting of a frank nature. In such cases the patient is obviously being overwhelmed by a rapidly progressing toxæmia and is reduced to a dangerous condition of health in a few days or weeks.

The imposition of an embryo, the destructive phenomena of the process of its embedding, and the needs for its development upon the metabolism of its mother hostess produce such a disturbance that in most women the resulting toxæmia is manifested by the vomiting of pregnancy. Fortunately, the majority of women are capable, by some adjustment of their metabolism, of their endocrines, or of both, of reestablishing a proper balance with relief from vomiting. The residue, however, pass into a state of persistent and dangerous sickness or are overwhelmed from the start with a toxæmia so grave that life is endangered in a short time. It is with these cases that this article is concerned.

First to be considered is the woman who suffers from what is apparently the usual vomiting of pregnancy, but who does not after a few weeks improve spontaneously or in response to simple advice and treatment. Instead, the vomiting persists and becomes increasingly severe. Such patients remain surprisingly well, have few complaints, and do not appear to be suffering any serious ill effects. They may, however, go progressively down hill or may, with dramatic suddenness, become severely toxæmic and dangerously ill. The loss of fluid by urine and vomit is greater than the fluid intake and the body becomes dehydrated. There is a reduction in blood volume, with a concomitant apparent erythrocytosis. When the blood density is increased to a sufficient degree, there is a breakdown of the blood proteins, serum albumin and serum globulin, with the result that poisonous protein end products are added to the initial toxins of pregnancy. When this occurs the woman is in a dangerous state and it is not easy to treat her with success. On the other hand, if adequate treatment is instituted before the dehydration has become so marked that protein destruction is initiated, the outlook is much more favourable.

In the earlier stages of hyperemesis physical and biochemical investigations do not give much assistance. The blood chemistry is little changed; the urine is reduced in volume, the excretion of nitrogen as ammonia is increased, and ketones are usually present, the presence of acetone and diacetic acid being the result of starvation and thus only indirectly a result of the toxæmia. Signs of kidney damage, albuminuria, casts *et cetera*, are not usual, and the pulse and temperature are within normal limits. The dehydration is the key to the treatment. The patient must be given fluids much in excess of her output. In order to combat the ketosis a 5% solution of glucose is the most suitable fluid to use.

The outline of treatment is as follows:

1. Treatment in hospital is essential to remove the patient from her domestic environment and influences. The nurse should be one well trained and informed of the needs of the case. A copious enema should be given.

2. All solid food should be withheld for twenty-four hours, but a 5% glucose solution flavoured with lemon should be given by mouth in as large quantities as can be tolerated.

3. A sedative should be given at night, and for this purpose "Amytal" will be found satisfactory.

4. The intake and output of fluid must be carefully recorded.

5. The urine must be regularly examined.

6. At the end of twenty-four hours additions may be made to the diet: toast with jam or honey, but not butter, carbohydrates in the form of cereals, fruit juice, and gelatine preparations. With continued improvement the diet can be rapidly increased, and in favourable cases the patient will be taking regular four-hourly meals in the course of three or four days. Proteins, fats and chlorides should be restricted.

7. In cases in which the vomiting prevents fluid intake by mouth, the glucose solution must be given by other routes: three-hourly ten ounce rectal drinks, subcutaneous injections, and in severe cases intravenous introduction of fluids. It is most important that the fluid intake should be at least double the output in order to overtake as rapidly as possible the dehydration.

8. The psychological factor must not be overlooked. Preparations for vomiting, such as basins and towels, should be removed from the patient as soon and as far as possible, discussion of the case should not be conducted in the patient's presence, vigorous treatment should be diminished as soon as conditions permit, and an atmosphere of confidence created by nurses and medical attendants.

9. The patient should remain in hospital until she is able to take ordinary meals, walk about freely, and in public hospitals take some share in the minor domestic duties of the ward. Too early return home is very apt to be followed by a recurrence of the vomiting.

10. Favourable signs are the cessation of sickness, improvement in appearance with loss of anxiety, moister tongue, increased diuresis, disappearance of ketones from the urine, natural sleep, and improvement in mental composure.

The majority of cases respond to treatment along these lines and the pregnancy proceeds in a satisfactory manner, but some patients will deteriorate in spite of thorough and skilful management. The question of terminating the pregnancy will then arise. Allowing that every case must be treated on its merits, the following may be regarded as indications for the serious consideration of the question of emptying the uterus: (i) persistence of the vomiting, (ii) serious loss of weight, (iii) persistence of low urine volume, (iv) fluid output exceeding fluid intake, (v) persistence of acetone and diacetic acid in the urine, (vi) albuminuria with casts, (vii) pulse rate persistently over 100, (viii) temperature persistently over 37·8° C. (100° F.), (ix) inevitable spontaneous abortion.

There remain to be considered the graver cases which may result from prolonged dehydration or may from the outset be due to an overwhelming toxæmia.

The phenomena are similar, whether they arise *ab initio* or as sequelæ. The patient is obviously toxæmic, she has an anxious, worried expression; she rapidly loses weight; she vomits persistently, the ejection becoming coffee

ground, bilious or even fæcal; the pulse and temperature are raised; the urine is scanty, highly coloured, loaded with ketones, albumin, casts and sometimes bile; the patient is restless and sleepless; and finally signs of mental disturbance, such as confusion, delirium and coma, appear. Such patients do not respond to treatment and can seldom be saved, except by prompt evacuation of the uterus. If the graver symptoms, and especially icterus and urinary bile, have not appeared, intensive treatment by a forced fluid intake by intravenous infusion may be tried, but in the absence of prompt improvement abortion should be procured. It is most important to bear in mind the fact that if these patients are allowed to deteriorate too far, even emptying the uterus will be of no avail, as the destruction of kidney and liver substance will have been so great that death will supervene after operation.

It is seldom that the milder cases cannot be satisfactorily treated and abortion obviated, but it is most unwise to delay evacuation of the uterus in cases that manifest the symptoms of grave import.

Toxæmias of Late Pregnancy.

The attitude of the obstetrician to the problems of the toxæmic woman has undergone considerable adjustment during the past five years. This has been necessary because of the investigations made into the health of toxæmic patients subsequent to their morbid pregnancies. The establishment of post-natal clinics and careful "follow-up" of such women has compelled us to revise not only accepted views upon the destiny of toxæmics, but also our treatment.

Until quite recently erroneous statements survived in the text books—statements that the toxæmic woman made a complete recovery after delivery or even that one attack of eclampsia conferred some measure of immunity against similar complication in future pregnancies.

The work of Young in Edinburgh, Gibberd in London, and Peckham and Stout of Baltimore has completely exploded that pleasant and convenient fallacy. The striking concurrence of opinion arrived at independently by these three groups of workers emphasizes the importance and accuracy of their findings.

Thus Gibberd states that of every 100 women suffering from toxæmia of pregnancy 40 make a complete recovery, 50 suffer some degree of permanent kidney damage which will be manifest in subsequent pregnancies, 10 suffer from a permanent chronic nephritis.

Further, the ten women who are left with chronic nephritis passed albumin prior to delivery for an average period of nine weeks. Of women who pass albumin for three weeks or more prior to delivery, 70% show albuminuria in subsequent pregnancies, whereas of those who pass albumin for three weeks or less, only 40% have a similar recurrence. These rather startling and illuminating facts clearly indicate that we have more to consider than the immediate risk to life. It cannot be considered to be good obstetrics to pilot a patient through a precarious pregnancy, only to leave her with a permanently lowered kidney reserve.

We must estimate our results in terms of maternal morbidity and not merely in terms of maternal mortality.

We are faced by the fact that hitherto 60% of toxæmic women have suffered some degree of permanent kidney damage and that the severity of this damage is in direct ratio to the duration of the albuminuria prior to delivery.

The dangerous terminal phenomena of toxæmias of pregnancy must be regarded as preventible by proper ante-natal care; in point of fact the detection of these states and their early treatment is the most promising side of ante-natal service. It is the experience of most clinics that eclampsia is steadily disappearing concurrently with the increase and thoroughness of supervision during pregnancy.

By means of the coarser laboratory tests for albuminuria, such as boiling and acidulation, it will be found that about 5% of pregnant women show albumin in their urine, the incidence being higher in *primigravidæ*. It is believed that this is due to a toxin which, being a peculiar product of conception, is generally supposed to be derived from some fœtal structure, probably the placenta or villi.

The origin of the toxin is still a matter of dispute and uncertainty; in fact Whitridge Williams mentioned no less than twelve hypotheses that have been promulgated to explain the source of the poison. Whatever may be the cause, we may assume that in certain pregnant women deleterious materials are produced which lead to a toxæmic state and to more or less destruction of the parenchyma of viscera. Since the liver is the detoxicating and the kidneys are the excretory organs, it is upon these viscera that the brunt of the poison falls. Classification of cases of toxæmia of pregnancy is difficult; in all probability the ætiology is the same and the variation merely one of degree of severity of the poisoned state. It has been aptly stated that "all pregnant women are slightly toxic", but, fortunately, the majority, by the natural protective powers of the body, are able to overcome or successfully to antagonize the virus. Others are less fortunate and manifest signs of toxæmia. The milder forms, classed by Stander and Peckham as cases of "low reserve kidney", form a fairly definite class.

1. *Mild Toxæmic Conditions Associated with Pregnancy.*

In mild toxæmic conditions the albuminuria does not appear until the last two months of pregnancy. There is usually some slight œdema confined to the ankles; the blood pressure remains in the limits of 150 millimetres of mercury systolic and 90 diastolic, the subjective symptoms are absent or slight. There may be some headache, but it is frequently no more marked than the headaches to which most women are subject. The albumin is seldom more than two parts on the Esbach scale.

Blood nitrogen and urea concentration estimations are within normal limits. The prognosis in these cases is good. They respond readily to treatment, usually proceed to the birth of a healthy child at term, after delivery all evidence of toxæmia quickly disappears, and the subsequent health of the patient is unaffected. They share equally every woman's liability to have a similar condition in a future pregnancy, but they apparently run little risk of permanent kidney damage.

Treatment.—The treatment of these milder cases demands rest in bed, free purgation and restriction of diet. Saline aperients are the most satisfactory, a free dose of sulphate of magnesia or of soda being given each morning before food. Should salines disagree, the compound powder of jalap may be used in doses of 1·0 gramme (fifteen grains).

For two or three days the diet should be limited to fruit, milk and gelatine preparations; it may then be gradually increased under the control of frequent estimations of the urine and blood pressure. Most cases will respond with disappearance of the albumin and lowering of the blood pressure.

Occasionally response is slow or absent, and the albuminuria and the blood pressure persist or increase. When such failure occurs or an initial improvement is followed by relapse, it may be necessary to consider the question of inducing labour.

It has been pointed out that the continued passage of even small amounts of albumin is detrimental to the kidneys, and consideration for the mother's future health may fairly influence any decision for or against induction. The risk to the mother of induction of labour is not great, and a fœtus, say, of thirty-six weeks, stands a better chance after premature birth than it does in the uterus of a toxæmic mother.

2. *Preeclamptic Toxæmia.*

The difference between preeclamptic toxæmia and the first class of case is only one of degree; in fact a mild case can, if neglected, assume a graver aspect and pass into the second group. In this group the albuminuria is more marked, as much as ten or twelve parts Esbach; hyaline, granular and epithelial casts, and sometimes red blood cells are present in the urine.

The blood pressure is from 150 to 200 millimetres of mercury systolic and 100 to 130 diastolic. The œdema is more marked and may affect the hands, face and vulva. Occasionally surface œdema is difficult to detect, but undue increase in weight suggests water retention.

Biochemical investigations still show little change; there is no evidence of nitrogen retention; the nitrogen partition usually reveals an increased excretion as ammonia and uric acid, and the carbon dioxide combining power is reduced.

With unsatisfactory progress of such a case definite pre-convulsive symptoms may appear, such as intense headache, vomiting and severe epigastric pain, ocular symptoms, such as dimness of vision and amaurosis, marked diminution in urine volume, and mental disturbances.

3. *Eclampsia.*

The convulsive attack of eclampsia must be regarded as the end result of a toxæmic state that has received no or inadequate treatment or has failed to respond to treatment, or, on the other hand, as the rapid sequel to the so-called fulminant toxæmia. This latter is a severe toxæmia of very rapid onset and course characterized by grave symptoms from the start. Such cases show massive albuminuria, blood pressures rising as high as 250 millimetres of mercury, very scanty urine or even anuria, jaundice, blood and bile in the urine, grave ocular symptoms, marked œdema, restlessness and mental disturbance. This formidable array of clinical phenomena may appear with startling suddenness, but in all probability, had examinations been possible day by day, some warning of even these fulminant cases would have been received in the form of increased blood pressures or albuminuria.

The treatment of the actual eclamptic state has already been skilfully dealt with in these columns by Professor J. C. Windeyer (THE MEDICAL JOURNAL OF AUSTRALIA, August 5, 1933) and is moreover outside the scope of this article.

Other conservative methods of treatment are from time to time recommended, such as the exhibition of alkalis with calcium by mouth or intravenously, the use of calcium and glucose in the form of calcium gluconate, and the exploitation of various endocrine preparations.

These methods have each given satisfaction in the hands of workers, but none of them is sufficiently established to justify advocacy for common usage. The most promising is the alkali and calcium treatment, which is fully described by Cameron in *The Lancet* of October 1, 1932, and by Daly in *The Journal of Obstetrics and Gynæcology of the British Empire* of April, 1933.

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British Medical Association News.

SCIENTIFIC.

A MEETING OF THE TASMANIAN BRANCH OF THE BRITISH MEDICAL ASSOCIATION was held at the Tasmanian Museum on November 14, 1933, DR. STUART GIBSON, the Vice-President, in the chair.

The Treatment of Excessive Bleeding at the Menopause.

DR. FRANK FAY read a paper in which he discussed the surgical as opposed to the irradiation treatment of excessive bleeding of the menopause. He pointed out that in considering the question in this way they must not forget that the condition might be treated by drugs, glandular preparations and so forth. He intended, however, to deal with that class of case in which there had been no response to ordinary therapeutic measures. Patients in this class alone should be forced to seek relief either by surgical or irradiation methods.

Not infrequently patients about the age of forty-five years were sent to a surgeon for hysterectomy because of continued and uncontrollable uterine hæmorrhage. Frequently the blood count was low and the hæmoglobin value down to 50% or lower. The problem that confronted the surgeon was whether the patient would stand hysterectomy or not. It was found, however, that even debilitated patients stood hysterectomy well, provided a preliminary course of glucose and saline solution had been administered.

It had been the lot of most operators to perform hysterectomy, and after sectioning the removed organ to find neither polypoid degeneration of the endometrium nor any sign of fibromata, either submucoid or in any other vicinity. The removed organ was hard and unduly fibrous, the contractile muscular tissue having been replaced by a non-contractile fibrosis. This class of case caused one to pause and consider whether the correct procedure had been adopted.

It was suggested that with radium available this *contretemps* should rarely, if ever, occur.

Dr. Fay referred to a lecture recently delivered by Dr. Keith Vartan, in which he stated that since its introduction into therapeutics radium had enjoyed a varying popularity, at first being treated with scepticism and later heralded as a panacea for all ills; it was only within the last few years, as a result of careful observation by a number of clinicians all over the world, that its correct value was becoming appreciated.

The non-malignant gynæcological conditions for which radium had the most value were: (i) suppression of irregular uterine hæmorrhage, (ii) fibroids, (iii) certain cases of intrinsic dysmenorrhœa, (iv) certain cases of endometritis.

The therapeutic use of radium was based on two main facts: (i) that its effect varied inversely as the square of the distance, and its effect was therefore essentially local, (ii) that the more embryonic and the more active the cell, the more sensitive was it to radium.

That radium suppressed menstruation was known, but did it do so by acting on the endometrium or on the ovaries?

The supporters of the one school of thought alleged that radium converted endometrium into connective tissue and necrosis was caused by secondary rays improperly screened, which led to healing and obliteration of the endometrial cavity. To support this they stated that only 20% of women showed menopausal symptoms, and also that in assuming that the ovaries had been affected the German school had failed to recognize that the normal ovary was situated three and a half inches from the uterus and to apply the law of the inverse square to this case.

The German school, however, believed the ovaries to be affected on the following grounds: (i) There was microscopic evidence of more or less complete destruction of Graafian follicles, with fibrosis of the interstitial tissue and atrophy of the whole organ; (ii) the cells themselves showed cloudy swelling, vacuolation, shrinking and ultimate replacement by fibrous tissue. This view was not without its clinical support, for it was not uncommon for a patient to have one or two menstrual periods before cessation; and sometimes, after a prolonged period of amenorrhœa, the menses might recommence. Now on the theory of fibrosis of the endometrial cavity it would be possible to explain the gradual suppression of menstruation, but it was not possible to explain its recommencement. If, however, one assumed the ovary to be affected, then the following explanation was forthcoming.

Radium was given, and all actively growing follicles were destroyed. One or two, however, were on the point of rupturing, and did so, causing one or two periods. After a prolonged period of amenorrhœa, follicles which previously were dormant, and not undergoing sufficiently active metabolism to be destroyed by radium, matured and reestablished menstruation.

The balance of present day opinion was in favour of the latter view.

Before radium was given to suppress irregular hæmorrhage the full potential significance of the bleeding must be realized. In order to do this it was essential first to exclude the hæmorrhages associated with pregnancy and then by physical examination to exclude carcinoma, submucous fibroids, retained products, adenomata, and a variety of other conditions. If after these investigations nothing was found, one might assume that endocrine imbalance was the cause, and treat it accordingly, namely,

by suppressing the action of the ovary, subject to one very important consideration—the age of the patient. If the patient was below forty, then the menopausal symptoms, headache, flushings and sweatings, were apt to be severe. Therefore the creation of a permanent and abrupt menopause below this age was undesirable. Between the ages of forty and forty-three it was well to be guarded in giving a prognosis of the after-effects. After this age irradiation was indicated.

It was obvious that in an otherwise healthy subject under the age of forty the aim would not be to produce an artificial menopause, as would be the case in women over forty-five, but merely to give sufficient dosage only partially to inhibit ovarian activity.

After describing Vartan's technique Dr. Fay said that the sequelæ of the radium therapy had been worked out by Dr. Donaldson at Saint Bartholomew's Hospital in a series of 100 cases. Only 15 patients had no menopausal symptoms, 50 put on weight, only 7 had dyspareunia. The last point suggested that the criticism that radium scarred the vagina was unjustified.

The end results of a series collected by Asherson at University College Hospital in a series of 63 cases were that 55 patients were cured with one application, 6 required a second application, 2 were untraced. Asherson also had figures for cases in which radium was given to people below the age of forty in order to produce a temporary menopause. Twenty-three patients were treated. Sixteen were restored to normal menstruation after a short period.

The difficulty in these cases was to be sure that a temporary and not a permanent menopause was going to be caused. The dose was 50 milligrammes and the time varied between 8 and 50 hours. An observation arose out of this, namely, that the younger the patient, the greater the dose necessary to produce amenorrhœa.

Turning to the position radium occupied in the treatment of fibroids, Dr. Fay pointed out that women over the age of forty with small fibroids, if they did not wish to undergo a major surgical procedure, were no longer compelled to await the menopause, a process which was slow and incapacitating. Instead, by means of irradiation, suppression of menstruation could be made to occur and the patient could be thus relieved.

As with everything else, however, there were rules which governed the use of radium in cases of fibroids: (i) The patient must be over forty years of age. (ii) Hæmorrhage must be the cardinal symptom. (iii) There must be no pressure symptoms. (iv) The fibroids must not be pedunculated. (v) There must be no sign of degeneration. (vi) No pelvic inflammation must be present. It would be seen by this list that the field was considerably limited.

Dr. Fay then discussed the objections to using radium and enumerated them under the following headings.

1. Although the hæmorrhage would be controlled and the fibroid shrink, yet the fibroid would not disappear; it might even grow again. Then it might degenerate, and in fact it was more likely to degenerate after radium, for the blood supply was interfered with. This explained why submucous fibroids should not be treated with radium—sloughing was almost certain to occur.

2. Malignant change might be overlooked. It had occurred in 6% in one series (Polak).

3. A large proportion of fibroids were accompanied by tubo-ovarian disease in some form or another; this figure was placed as high as 50% by some observers.

4. The inflammatory reaction which radium always caused might light up any latent adnexal inflammation which previously might have been entirely unsuspected.

5. Pressure symptoms were not relieved.

The advantages that radium could offer over surgery were the following:

1. There was no mortality.

2. Should radium not be satisfactory, surgery could still be fallen back upon.

3. Radium definitely was the treatment of choice when the patient was what was known as a poor operative risk—suffering from carditis, chronic nephritis or diabetes uncontrolled by insulin.

In one series of cases 206 patients were treated. Two hundred ceased menstruating and were relieved of symptoms. In the remaining six cases surgery had to be used, and in each case it was because the condition in the first place had been unsuited to radium, submucous fibroids subsequently being found on each occasion. In 130 of these same cases the tumour had shrunk to half its original size, and in 70 of them, to all intents and purposes, it had disappeared.

The last condition for which radium had been and was being satisfactorily used was primary intrinsic dysmenorrhœa. This was a condition in which the dysmenorrhœa was part of the clinical picture of a general hypoplasia of the genitalia. There were two main types: (i) the anteflexed, reposited uterus with a small cervix; (ii) a uterus with acute forward or backward flexion.

In these cases, when the standard and time-worn remedies had been tried, the cervix might be gradually dilated with Hegar's graduated sounds and a fifty milligramme radium tube was then inserted high up into the body of the uterus and was left there for four hours. Menstruation was not stopped, but dysmenorrhœa was relieved.

Dr. Fay asked whether this was simply mechanical or psychological, or was it that the ovary had in some way been stimulated. A satisfactory explanation was not yet available, but if figures were required Polak's series could not be bettered. In 36 cases there were 36 cures; nine patients had subsequently become pregnant and six had live children.

In addition to those more well established conditions for which radium had been used, there were one or two others, for instance, the diffuse adenomyoma such as occurred in the recto-vaginal septum, and which would be beyond the bounds of prudent surgery. Small doses of radium had been used, too, in cases of amenorrhœa in the hope of stimulating the flagging ovary.

Dr. Fay said in conclusion that the technique adopted in the series of fourteen cases, the results of which had prompted his paper, was as follows: Twenty milligrammes of radium were screened by 0·5 millimetre of platinum and 2·0 millimetres of rubber were inserted beyond the cervix into the fundus of the uterus. This not only avoided stricture of the cervix, but it avoided burning the vagina. The radium was left in position for 100 hours, thus making a total treatment of 2,000 milligramme-hours. Vartan's milligramme-hours worked out (taking his optimum time as 48 hours) at 2,400 milligramme-hours, or 400 milligramme-hours more than Dr. Fay had been using. In a few cases, however, 25 milligrammes of radium had been used for 100 hours, resulting in 2,500 milligramme-hours, being slightly in excess of Vartan's optimum dose.

Although the number of cases in the series treated was only fourteen and the time varied only from two and a half years to six weeks before the meeting, the results had been sufficiently striking to warrant a belief that radium treatment of menorrhagia must henceforth definitely be included in the armamentarium of the gynæcologist.

DR. E. BRETTINGHAM MOORE congratulated Dr. Fay upon his paper. He wished to know whether X rays could replace radium in the treatment of such conditions. He was surprised that Dr. Fay had included diabetes among the contraindications to irradiation of the uterus. He did not agree that such treatment carried no risk of death. He asked if Dr. Fay had had any experience of the treatment by radium of young women who suffered from excessive bleeding at the menses.

DR. T. GIBLIN added his congratulations to Dr. Fay. He pointed out that a patient, before being submitted to such treatment, should have her uterus curetted, so that the presence of malignant disease could be excluded by microscopic examination of the portions of endometrium removed. After such curettage a fortnight should be allowed to elapse to allow the endometrium to heal before radium was implanted.

DR. E. W. J. IRELAND expressed his interest in Dr. Fay's paper. He had known of a patient who had undergone

complete bilateral oophorectomy. After the operation her metrorrhagia had recurred. It had then been cured by radium.

DR. E. A. ROGERS was of the opinion that such treatment carried a distinct risk of streptococcal infection of the uterus. He suggested that in order to avoid this the vagina should be packed with gauze soaked in anti-streptococcal serum.

Dr. Fay thanked the speakers for their kind reception of his paper. In reply to Dr. Moore he stated that X rays had the same action as radium. When he had mentioned diabetes as a contraindication to treatment he had had in mind patients whose disease could not be controlled by insulin. Perhaps he had been unguarded in his statement that irradiation treatment carried no mortality. It would have been perhaps safer to say that the number of deaths resulting from it was negligible compared with that resulting from surgery. He had had no experience of the treatment by radium of young women with menorrhagia, but a distinguished British gynæcologist had informed him that he had once unfortunately produced a permanent menopause in such a patient with a dose of 1,500 milligramme-hours. The case quoted by Dr. Ireland was a most important one. If the facts were as stated, it lent very strong support to the school which claimed that radium produced its effects by its action on the endometrium and not on the ovaries. He did not share Dr. Rogers's fears about streptococcal infection. The implantation of radium by a competent surgeon was no more likely to cause this than was the insertion of a self-returning pessary.

A MEETING OF THE VICTORIAN BRANCH OF THE BRITISH MEDICAL ASSOCIATION was held at Saint Vincent's Hospital, Melbourne, on August 16, 1933. The meeting took the form of a series of clinical demonstrations by members of the honorary staff.

Mikulicz's Disease.

DR. L. S. LATHAM showed a girl, aged sixteen years, who was suffering from Mikulicz's disease. The history extended over three months. The illness commenced with swelling in the region of both parotid, submaxillary, sublingual and lachrymal glands. Dryness of the mouth was present to a slight degree in the early stages only. On admission to hospital in July the patient's colour was noted to be good, the upper eyelids appeared full, swelling of lachrymal glands was detectable, but was reported by her medical attendant to be less than formerly. Decided enlargement of parotid, submaxillary and sublingual glands on the right and left sides, in which numerous separate nodules could be identified, was present. There were many enlarged lymphatic glands in the right and left sides of the neck and in the axillæ and groins. Both breasts showed numerous nodules lying among the glandular tissue, movable, but not tender, and presumably similar to those in the salivary glands. There was no enlargement of the spleen. An excised inguinal gland showed on section a field packed with lymphoid cells of monotonous type without follicular arrangement and resembling lymphosarcoma. The Wassermann test gave no reaction. The blood showed no evidence of lymphatic leuchæmia, the white cells being 4,600 per cubic millimetre and the differential count normal. Red cells numbered 4,500,000 per cubic millimetre, and the hæmoglobin value was 85%. A selected area on the right side of the neck had been submitted to a single treatment by X rays and a notable diminution in the glandular masses of that area had followed.

Malignant Stricture of the Œsophagus.

DR. F. E. MCAREE showed a male, aged sixty-two years, who for the past two months had noticed that food seemed to "stick" a little above the lower end of the sternum. Lately, if he took solid food he had to make himself vomit to get any comfort. He could still take fluids without trouble. He had been getting much weaker and had lost a stone in weight. No vomiting occurred unless it was self-induced. His previous health had been good. He denied venereal infection.

On examination he was a pale and somewhat emaciated man. The heart was a little enlarged; the sounds were clear. The lungs were clear. The abdomen was somewhat retracted; but nothing abnormal could be felt. One small, hard gland was palpable in the left supraclavicular fossa. X ray examination disclosed a definite hold-up in the lower end of the œsophagus with marked dilatation. The outline of the stricture was very irregular, indicating a neoplasm with involvement of surrounding structures.

Secondary Carcinoma of the Liver.

Dr. McAree's second patient was a woman aged fifty-two. She had not felt well for six months. For the past six weeks she had noticed increasing swelling of the abdomen, with some dyspnœa. She did not vomit. She had lost nearly a stone in weight. She gave a history of "bleeding piles" for the past two years. The menopause occurred three years ago.

On examination she was a very anæmic woman. The heart action was forcible, with occasional extrasystoles; a hæmic systolic bruit was audible over the base of the heart. The abdomen was very distended, with marked ascites. On deep pressure a hard, irregular mass could be felt 5·0 centimetres (two inches) below the right costal margin, moving with respiration and almost certainly the lower border of the liver. The spleen was not palpable. The blood picture was that of secondary anæmia. Pelvic and rectal examinations revealed no abnormality. A barium meal revealed a normal stomach. The urine and fæces both contained bile. Dr. McAree thought the primary growth was located somewhere in the bowel.

A Case for Thoracoplasty.

DR. W. J. NEWING demonstrated a patient who was, in his opinion, suitable for thoracoplasty. A woman, aged twenty-seven years, four years previously had an extensive tuberculous bronchopneumonia which appeared to involve the whole of the right lung. After a short period of rapid downward progress artificial pneumothorax was performed. This arrested the process and within six months the patient was restored to comparative health and remained so until recently, when hæmorrhage commenced. The reason for this was a gradual obliteration of the air space by creeping of the pleura, that is, progressive adherence of the visceral and parietal pleuræ, spreading from below upwards and allowing reexpansion of the underlying lung. This process, which was not an uncommon one in compression cases, commenced about eighteen months ago and had allowed the lower lobe to reexpand. The patient had had two small hæmorrhages in the past four months, and Dr. Newing thought a recurrence inevitable unless surgical collapse was instituted. The patient was in excellent general condition and afebrile.

Familial Acholuric Jaundice.

Dr. Newing's second case was one of familial acholuric jaundice with unusual features. A married woman, aged twenty-eight years, was born jaundiced. One brother was jaundiced, the rest of the family were healthy. The patient's complaint was weakness, which appeared to be mainly the result of under-nourishment. At nō period in her life had she complained of symptoms referable to the disturbance of her hæmoglobin metabolism.

Apart from the fact that she was deeply jaundiced and the urine was bile-free, the usual accompaniments of this disease were entirely absent. There was no splenic enlargement; the red and white blood counts, hæmoglobin percentage, corpuscle fragility and reticulocyte count were all normal. The stools were brown. The Van den Bergh test gave an indirect positive reaction.

These results were identical with those obtained eight years before by Dr. S. O. Cowen during a survey of the same patient. Some obscure changes were taking place, however, in that during the last two or three years there had occurred several attacks of pain in the region of the liver, accompanied by shivering, during which she became

more deeply jaundiced and the urine became dark. Dr. F. D'Arcy suggested that this might be due to the development of pigment stones in the common duct. No satisfactory explanation was offered for the curious disturbance of hæmoglobin metabolism.

Diabetes Mellitus.

DR. T. A. F. HEALE showed four diabetic patients who had been treated with liberal carbohydrate diets. The first patient was a female, aged sixty-one years, who was first seen in October, 1931. The usual diabetic symptoms had been present for some months. The urine contained a large amount of sugar and a trace of ketones. The fasting blood sugar was 0·21%. The patient had received no previous treatment. She was placed on a diet of carbohydrate 99 grammes, protein 61 grammes, fat 78 grammes, calories 1,342. The urine became sugar-free within a week. No insulin was used. When the blood sugar had reached the normal level the diet was gradually increased. Now the patient was well and the urine was constantly sugar-free on a diet of carbohydrate 172 grammes, protein 73 grammes, fat 88 grammes, calories 1,774, without insulin. The fasting blood sugar was 0·10%.

The second patient was a female, aged thirty-eight years, who was first seen in February, 1933. The classical diabetic symptoms had appeared two months previously. The urine contained a large amount of sugar and a moderate amount of ketones. The fasting blood sugar was 0·19%. She had had no previous treatment. She was discharged from hospital on a diet of carbohydrate 170 grammes, protein 69 grammes, fat 70 grammes, calories 1,596, with insulin 30 units daily (18 units before breakfast and 12 units before the evening meal). The fasting blood sugar was 0·12%. At present she was well and the urine was constantly sugar-free on a diet of carbohydrate 187 grammes, protein 75 grammes, fat 80 grammes, calories 1,768, with insulin 12 units daily (six units before breakfast and six units before the evening meal). The fasting blood sugar was 0·10%.

The third patient was a male, aged thirty-eight years, who was admitted to hospital in June, 1932. The usual diabetic symptoms had been present for four months. The urine contained a large amount of sugar and a trace of ketones. The fasting blood sugar was 0·23%. He had had no previous treatment. He was discharged from hospital on a diet of carbohydrate 256 grammes, protein 82 grammes, fat 78 grammes, calories 2,054, with insulin 78 units daily (36 units before breakfast, 21 units before lunch, and 21 units before the evening meal). The fasting blood sugar was 0·11%. Now he was well and constantly sugar-free on a diet of carbohydrate 268 grammes, protein 84 grammes, fat 76 grammes, calories 2,092, with insulin 45 units daily (27 units before breakfast and 18 units before the evening meal). The fasting blood sugar was 0·09%.

The fourth patient was a male, aged eighteen years, who was first seen in November, 1929. *Diabetes mellitus* developed early in 1929 at the age of thirteen and a half years. He was treated with diet and insulin and at his first attendance his urine was sugar-free on a diet of carbohydrate 75 grammes, protein 75 grammes, fat 150 grammes, calories 1,950, with five units of insulin daily, the insulin being given before breakfast. The fasting blood sugar was 0·09%. During 1930 the urine remained sugar-free on diet alone. Early in 1931, with the onset of a "cold in the head", glycosuria returned, and even after he had recovered from the infection large doses of insulin were needed to control the diabetes. Ultimately, on a diet of carbohydrate 150 grammes, protein 75 grammes, fat 80 grammes, calories 1,620, his urine remained sugar-free with 60 units of insulin daily (30 units before breakfast and 30 units before the evening meal). The fasting blood sugar was 0·12%. His tonsils and adenoids were removed at this stage and convalescence was uneventful. He then began diet breaking, adding considerable amounts of bread to the prescribed diet. His diet was then changed to one containing carbohydrate 105 grammes, protein 75 grammes, fat 135 grammes, calories 1,915. He required 114 units of insulin (60 units before breakfast and 54 units before the evening meal) to keep the urine sugar-free. During 1932 his diet was gradually altered to contain more carbohydrate and less fat. Now he was on a diet of carbohydrate 194 grammes, protein 87 grammes, fat 78 grammes, calories 1,826, with insulin 30 units daily (18 units before breakfast and 12 units before the evening meal). The urine was constantly sugar-free and the fasting blood sugar was 0·095%.

Dr. Heale said that he showed these patients because he felt that the important change which had taken place in recent years in the diabetic diet was not as widely known as it should be. Most doctors still used the classic low carbohydrate-high fat diet. This type of diet had proved satisfactory in the past for many diabetic patients, but it was admittedly an abnormal diet. The newer liberal carbohydrate diet conformed more nearly to the diet of normal people, and it seemed more rational to tend towards rather than deviate from the normal standard. Dr. Heale said that he had been using the higher carbohydrate-lower fat diets for the past two and a half years, and was convinced that this type of diet for diabetics had come to stay. On this diet patients had felt fitter and looked fitter than they had on the older diet; the choice of foods was wider, all foods except sugar and foods sweetened with it now being allowed; and, finally, control of the diabetes was attained and maintained without difficulty.

Dr. Heale said that authorities differed somewhat in the amounts of carbohydrate and fat they prescribed. At present it was not possible to state positively the optimum amounts of carbohydrate and fat. The future alone would settle the problem. In any case the standard range of values would be a fairly wide one, because each patient had his own individual requirements. Dr. Heale said that in his own series of cases the partition of the diet had varied considerably. The amount of carbohydrate had ranged from 100 to 490 grammes. Most of his patients were receiving 140 to 200 grammes; quite a number were taking 200 to 300 grammes, but so far only a few patients were taking over 300 grammes. He had not used less than 100 grammes of carbohydrate, and few patients had remained on only 100 grammes of carbohydrate, except for a short time at the beginning of treatment. The upper limit of the fat ration had been fixed arbitrarily at 100 grammes; from 70 to 90 grammes were usually given. The protein allowance was adequate and had ranged from 55 to 100 grammes. All patients received a diet which was adequate for the type of life they wished to lead. Adequate nutrition, but not over-nutrition, was a fundamental principle.

Dr. Heale said that at present 70% of his patients were using insulin and 30% were not. The average daily dose of insulin was 36 units. Many critics of the liberal carbohydrate diets seemed to think that all patients so treated would require insulin and in large amounts. This was not so, as the above figures showed. Some authorities, notably Geyelin of New York, advocated the routine use of insulin for all diabetics. Dr. Heale did not go so far as this, but he did not believe in stinting insulin. There were many diabetics not using insulin at present who would do better if they were using it. Patients often objected to the use of insulin, but in his experience only rarely did they wish to give it up once they had experienced its benefits. Apart from the emergency use of insulin, Dr. Heale said that he advised insulin for: (*a*) all diabetic children and adolescents, (*b*) all young adult diabetics and all patients with acute and severe diabetes at any age, (*c*) all diabetics at any age who were unable to take an adequate diet without insulin.

The majority of his own patients had done well on two doses of insulin a day, one in the morning and one in the evening. A moderate number were receiving three doses a day; most of these had an injection before breakfast and before the evening meal, the third dose being taken on retiring, about 10 to 11 p.m. This last dose was a small one, usually two to eight units. A few patients injected their insulin before breakfast, lunch and evening meal. The most satisfactory balance between diet and

insulin was found out by experiment; the aim was to maintain a sugar-free urine and a normal range of blood sugar.

Dr. Heale said that almost always, when a patient taking a low carbohydrate-high fat diet was first transferred to a liberal carbohydrate-low fat diet, glycosuria returned. This upset was temporary only, but might last days, weeks, or even months, and was therefore rather disconcerting. During this period the insulin dose had to be raised, often considerably; eventually, however, improvement in tolerance followed and the insulin dose was then no greater than it had been on the old diet, and sometimes even less. It was important, therefore, to know about this upset and thus avoid getting into a panic.

Dr. Heale quoted the record of one patient, a male aged twenty-eight years. When first seen, he was on a diet of carbohydrate 25 grammes, protein 91 grammes, fat 168 grammes, calories 1,976, with insulin 27 units daily. He was transferred to a diet of carbohydrate 187 grammes, protein 75 grammes, fat 80 grammes, calories 1,768, with insulin 28 units daily. Glycosuria returned and persisted for ten days. The urine then became sugar-free without further alteration in the insulin dose. Now his urine was sugar-free on a diet of carbohydrate 304 grammes, protein 85 grammes, fat 91 grammes, calories 2,375, with 24 units of insulin daily. The fasting blood sugar was normal.

Dr. Heale used a series of standard diets which simplified treatment at the beginning. The patient was prescribed a suitable standard diet until his individual requirements could be determined. A special diet was then arranged to meet his particular needs. A copy of the standard diets was shown. All the diets were calculated according to Joslin's well known table of food values. These values were sufficiently accurate for all clinical purposes, and patients whose diets were constructed with the aid of these food values did well. There was no advantage in using the more recent Lawrence and McCance values for vegetables and fruits.

Osteoporosis of the Radius.

DR. THOMAS KING demonstrated a case of traumatic painful osteoporosis at the lower end of the radius. The patient was seventy years of age, and eight months ago was treated for a Colles's fracture. The fracture was excellently reduced, immobilized with a dorsal plaster splint for four weeks, and during the whole time the patient attended the physiotherapy department for daily supervision of physical exercises. None the less, despite ideal treatment, she developed stiffness of the fingers and obvious trophic changes of the bones, skin, nails, subcutaneous tissues and peripheral joints. There was no nerve lesion. Pain was a special feature. X ray examination after seven months revealed marked osteoporosis. The hand and wrist were hot and swollen. The skin was discoloured. Following the teaching of Leriche, a brachial artery periarterial sympathectomy (one cubic centimetre of absolute alcohol was injected into the periarterial sheath) was performed and within three weeks the condition of the hand had almost returned to normal, pain having entirely disappeared.

Two other patients illustrating the same disabling condition were shown. In one the hand and wrist of the extremity were affected owing to a fracture of the neck of the scapula, in which the coracoid process and the underlying vasculo-nervous bundle were carried medially and had not been reduced. An axillary periarterial sympathectomy was in view.

Compression Fracture of the Os Calcis.

The other case was a bilateral compression fracture of both heel bones (*os calcis*). The same characteristic trophic changes were marked. The pain was so severe that the patient could not walk far at all. He was only forty years of age and the fractures, which were not reduced, had occurred fourteen months before. This case also illustrated what a crippling condition a fracture of the *os calcis* could produce. Another case of fractured *os calcis* was shown. It was of seventeen months' duration; no reduction had been carried out, with great crippling to the patient, who could not walk.

A cinematographic film was shown illustrating the treatment of fracture of the *os calcis* with the Phelps-Gocht clamp for the collapse of the bone and the upwards displacement of the posterior fragment, whilst Böhler's *os calcis* clamp was used for the broadening of the bone.

Physical Therapy in Fracture of the Spine.

Another cinematographic film was shown. It illustrated many exercises which patients with fractures of the spine are directed to perform daily in the physiotherapy department. These exercises were commenced almost immediately after the reduction of the fracture by hyperextension and immobilization in a plaster jacket. So strong did the muscles of the back become that the plaster jacket might be removed after fourteen weeks and no further orthopædic corset was necessary. The back was supple and often freer than before the injury, because during the whole time that the cast was immobilizing the injured spine they were exercising all muscles of the back and the whole body. Thereby painful stiffness, due to adhesions, muscle and ligamentous wasting, was avoided.

Genito-Urinary Tuberculosis.

DR. HENRY MORTENSEN presented two cases of genito-urinary tuberculosis.

A male patient, aged thirty-three years, in May, 1930, as a result of pleurisy with effusion, was diagnosed as suffering from pulmonary tuberculosis. In May, 1932, he was operated upon and his left testis and epididymis were removed for tuberculosis. In October, 1932, he reported again with a small sinus from the upper end of his operation wound and complaining also of pain in his right loin. Routine investigation disclosed no sign of his previous pulmonary disease; prostate, vesicles and right epididymis were normal, but tubercle bacilli were grown from his urine. Cystoscopy and pyelography disclosed a normal bladder and ureteric orifices, normal kidney function, indefinite excavation at the upper pole of his right kidney. He was placed on a course of tuberculin *R* and became symptom-free. His present condition showed a gain in weight of 4·09 kilograms (nine pounds) in two months. His present weight was 103·7 kilograms (sixteen stone two pounds). Tubercle bacilli were still present (the cultures made by Dr. Brenan were demonstrated). The pulmonary and genital systems were normal, the bladder was normal, but a definite excavation was present in the right pyelogram at the upper pole. Cultures at all times from either ureter have been negative.

DR. BASIL KILVINGTON, in the discussion that ensued on the treatment of this patient, agreed that, despite the present good general condition of this patient and his previous history of multiple tuberculous infections, a right nephrectomy was indicated.

The second patient presented was a male, aged thirty-six years, giving a four years' history of frequency of micturition and seeking advice concerning an attack of left-sided colic. Tubercle bacilli were cultured by Dr. A. Brenan in fourteen days from the urine. Cystoscopy revealed gross tuberculous involvement of the bladder with both ureters of the "golf hole" type. The right pyelogram showed a tuberculous involvement of the ulcero-cavernous type, whilst the left disclosed a hydronephrosis (arising in all probability from back working from the systolic bladder) with very slight evidence of tuberculous involvement.

Correspondence.

WORKERS' COMPENSATION PRACTICE IN NEW SOUTH WALES.

SIR: I am instructed to ask you to publish the following statement setting out the views of the Council of the British Medical Association, New South Wales Branch, in regard to fees payable to medical practitioners for attendance on injured workers entitled to the benefits of the *Workers' Compensation Act*, 1926-29.

The principle that industry should compensate injured workers by paying them a proportion of their wages while incapacitated and by providing the necessary medical and hospital services is now well recognized.

In New South Wales a *Workers' Compensation Act* has been in existence since 1910. Prior to 1926 no provision was made for medical benefits and the cost of hospital and medical treatment of any injury arising out of and in the course of his occupation had to be met by the worker himself. As a result the injured worker was often compelled, owing to his financial and physical circumstances, to seek treatment at the nearest public hospital as an indigent patient.

In 1926, however, the legislature, by amending the Act to provide that the compensation payable by the employer shall also include the cost of such medical, surgical and hospital treatment as may be reasonably required to relieve the worker of the injury, recognized not only the just claims of the worker, but also, with equal justice, the right of the medical profession to receive payment for services rendered to this class of patient.

In defining what shall be the liability of the employer for the cost of medical treatment of an injured worker, the 1926-29 *Workers' Compensation Act*, Section 10 (4) (*a*) provides, *inter alia*, that due regard must be had to "the customary charge made in the community for such treatment to persons other than workers".

In the opinion of the Council the wording of this particular clause of the section is quite definite and admits of no other interpretation than that the employer is liable to pay the worker, no matter what his earning capacity may be, reasonable medical expenses, due regard being had to the customary charges in private practice, that is, to the fees payable in the community to which the worker belongs.

In an article, "Medical Evidence, Certificates and Fees under the Workers' Compensation Act", in THE MEDICAL JOURNAL OF AUSTRALIA of December 9, 1933, Dr. R. M. Mackay, Chief Medical Referee and Medical Assessor of the Workers' Compensation Commission of New South Wales, states, when discussing the interpretation of Section 10 (4) (*a*), that: "the employer is only liable to indemnify the worker the cost of treatment which he (the worker) would otherwise be called upon to pay", meaning thereby that the ability of the worker himself to pay must be taken into consideration when determining what shall be the liability of the employer.

With such a contention the Council cannot possibly agree, for it implies a demand on the medical profession to give charity.

A medical practitioner is entitled to the full reward for his services. The fact that he waives his right to this reward in the case of those who, owing to their financial circumstances, are unable to pay in full, gives no right to the State or insurers or any other body to demand gratuitous service. Such a demand would be humiliating to the worker and unfair to the medical profession.

It was certainly never the intention of the legislature that the ability of the worker to pay should determine the liability of the employer for the cost of medical treatment. For, if this were so, there would have been no need to provide in the *Workers' Compensation Act* that the employer shall be liable to pay in addition to any compensation otherwise provided the cost of such medical or hospital treatment or ambulance service as may be reasonably necessary.

Dr. Mackay refers to cases in which there has apparently been overcharging by medical practitioners. It is not denied that some practitioners have failed to grasp the meaning of Section 10 (4) (*a*) and have made charges in excess of the employer's liability under the Act. Such cases, however, it can be definitely stated, have been the exception rather than the rule.

With reference to the case of the "fractured thigh" mentioned by Dr. Mackay, the practitioner was apparently in error, not in making the charge of twenty-one pounds, but in deciding that the thigh was fractured. If it was a fracture, no matter how simple, then the practitioner, in view of the arrangement, that is, Schedule "D", between the insurers and the Association, was fully entitled to his charge.

In this regard it may be pointed out that when Schedule "D" was drawn up and accepted by the Council it was understood that the fees therein represented average charges to apply without discrimination to all injured workers. During the latter part of last year a number of the insurers broke what we regarded as an agreement by drawing the attention of the Commission to the low wages of particular injured workers in order to have the fees reduced below the standard of Schedule "D".

There will always be differences of opinion between insurers and medical practitioners as to what is a reasonable charge. Realizing this, the Council has since 1927 provided free of cost to the insurers a means of arbitration in cases in which there has been difference of opinion as to the reasonableness or otherwise of practitioners' accounts. Where thought necessary the Council has not hesitated to reduce these accounts.

Referring to the cost of medical treatment, Dr. Mackay draws earnest attention to the figures of the Government Statistician, which show that the proportion of the cost of medical treatment to compensation payments to the worker has increased each year from 4·09% in 1926-1927 to 12·13% in 1931-1932. No reasons for this increase, however, are advanced by Dr. Mackay. Surely he does not mean that this increase is due to overcharging on the part of members of the medical profession.

There are many factors causing this increase. For example, to quote from Dr. Mackay's reference—the Sixth Annual Report of the Workers' Compensation Commission: "Some of the increase per case in the last three years may be due to the elimination of payment in all cases where the incapacity does not extend over seven days" (comment by the Government Statistician). Much of the increase can be ascribed to the fact that until the passing of the 1929 *Public Hospitals Act* many injured workers were treated in public hospitals free of charge because a member of the visiting medical staff of a public hospital was not permitted to charge a patient, no matter what his financial status might be, with any fees in respect of treatment. This injustice to members of the profession was remedied by the passing of the above mentioned Act. An injured worker admitted to a public hospital is now classified by the hospital authority as a paying patient and is required to pay the medical attendant for services rendered.

Moreover, has it not been the experience of every country that possesses workers' compensation or sickness insurance schemes that the number of claims made under such schemes has increased very considerably during the past few years? It is generally accepted that the main reason for this increase is that the benefits of such schemes are being demanded in full by those entitled to claim them.

In regard to the question of relative cost of medical treatment to compensation payments, it is interesting to note the experience of America, where practically every State has a workers' compensation act, the provisions of which are generally somewhat similar to those of the Act in New South Wales.

Dealing with this point, the National Industrial Conference Board of New York, in a publication, "Workers' Compensation Acts in the United States: The Medical Aspect", states: "Insurance rating bureaus advise that the medical expense of operating the compensation law averages approximately 15% of the total compensation. While the medical costs may seem in some instances to be high in relation to the amount of compensation paid, it is realized by both employers and insurance carriers that an increased medical cost, provided it represents an increasing quality of medical service, is a measure of economy, as it will cut down the amount of compensation paid."

As stated previously, by amending the Act to provide that the compensation payable by the employer shall also include the cost of such medical, surgical and hospital treatment as may be reasonably necessary, the legislature

recognized the right of the medical profession to receive payment for their services. There is, therefore, no question of diverting a large sum of money to the medical profession, as Dr. Mackay states. Rather, medical practitioners are being paid for services rendered.

Yours, etc.,

J. G. HUNTER,

Medical Secretary, New South Wales Branch of the British Medical Association.

British Medical Association House,
135, Macquarie Street,
Sydney,
January 5, 1933.

Obituary.

ROBERT WHITSON TELFORD.

WE regret to announce the death of Dr. Robert Whitson Telford, which occurred on January 1, 1934, at Ballarat, Victoria.

Books Received.

HUMAN EMBRYOLOGY AND MORPHOLOGY, by Sir Arthur Keith, M.D., F.R.S., LL.D., D.Sc., F.R.C.S.; Fifth Edition; 1933. London: Edward Arnold and Company. Royal 8vo., pp. 566, with illustrations. Price: 32s. 6d. net.

AN INTRODUCTION TO THE STUDY OF THE NERVOUS SYSTEM, by E. E. Hewer, D.Sc., and G. M. Sandes, F.R.C.S., M.B., B.S.; Second Edition; 1933. London: William Heinemann (Medical Books) Limited. Crown 4to., pp. 161, with illustrations. Price: 21s. net.

THE GREY BATTALION, by May Tilton; 1933. Australia: Angus and Robertson, Limited. Crown 8vo., pp. 310, with photographs. Price: 6s. net.

Medical Appointments Vacant, etc.

For announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser", pages xvi, xvii and xix.

AUSTIN HOSPITAL FOR CANCER AND CHRONIC DISEASES, HEIDELBERG, VICTORIA: Resident Medical Officer.

DISTRICT HOSPITAL, KALGOORLIE, WESTERN AUSTRALIA: Resident Medical Officer.

HOBART PUBLIC HOSPITAL, HOBART, TASMANIA: Junior Resident Medical Officers.

LAUNCESTON PUBLIC HOSPITAL, LAUNCESTON, TASMANIA: Resident Medical Officer.

MARRERA BABIES' HOSPITAL, WOODVILLE, SOUTH AUSTRALIA: Honorary Relieving Medical Officer.

NEW SOUTH WALES MASONIC HOSPITAL, SYDNEY, NEW SOUTH WALES: Resident Medical Officer.

PERTH HOSPITAL, PERTH, WESTERN AUSTRALIA: Junior Resident Medical Officers.

ROYAL NORTH SHORE HOSPITAL OF SYDNEY, NEW SOUTH WALES: Honorary Officers.

SAINT VINCENT'S HOSPITAL, MELBOURNE, VICTORIA: Honorary Officers.

THE BRISBANE AND SOUTH COAST HOSPITALS BOARD, QUEENSLAND: Honorary Officers.

THE HORNSBY AND DISTRICT HOSPITAL, HORNSBY, NEW SOUTH WALES: Resident Medical Officer; Honorary Officers.

THE NORMANTON DISTRICT HOSPITAL, NORMANTON, QUEENSLAND: Medical Officer.

THE UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA: Assistant Radium Registrar.

VICTORIAN EYE AND EAR HOSPITAL, MELBOURNE, VICTORIA: Resident Surgeons.

Medical Appointments: Important Notice.

MEDICAL practitioners are requested not to apply for any appointment referred to in the following table without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCH.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 135, Macquarie Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Friendly Society Lodges at Casino. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries. Australian Prudential Association, Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. Building, Adelaide Street, Brisbane.	Brisbane Associated Friendly Societies' Medical Institute. Chillagoe Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL are advised, in their own interests, to submit a copy of their agreement to the Council before signing. Lower Burdekin District Hospital, Ayr.
SOUTH AUSTRALIAN: Secretary, 207, North Terrace, Adelaide.	Combined Friendly Societies, Clarendon and Kangarilla districts. All Lodge Appointments in South Australia. All Contract Practice Appointments in South Australia.
WESTERN AUSTRALIAN: Honorary Secretary, 205, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.
NEW ZEALAND (Wellington Division): Honorary Secretary, Wellington.	Friendly Society Lodges, Wellington, New Zealand.

Editorial Notices.

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